Arch. Pharm. Res. Vol. 17, No. 4, pp. 249-255, 1994

A Novel Synthetic Route to 11-Deoxyanthracycline AB Synthons

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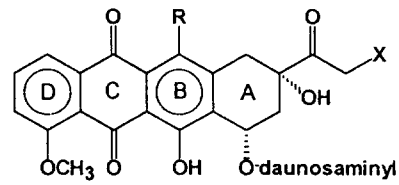
(Received April 28, 1994)

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 fuctionalized AB synthons **7** and **12**, respectively, via sequential epoxidation-reduction-protection processes.

Key words: 11-Deoxyanthracycline, 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.



R=OH, X=H: daunomycin
R=OH, X=OH: adriamycin
R=H, X=H: 11-deoxydaunomycin

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-

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mical 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 recored as λ_{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 benzophenone ketyl under an argon atmosphere. Dichloromethane, benzene, and dimethylforamide 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 (Perrin 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℃ 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℃ 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℃ over 60 min. The solution was stirred at 40 ℃ for 20min., 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 1.90 g (99%) of **1** as a brownish solid: mp 106℃ (recrystallized from ethyl acetate-hexane); IR(KBr) 1700; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 3.02 (m, 4H), 3.88 (s, 3H), 7.07 (d, J=8.0 Hz, 1H), 7.34 (dd, J=8.4, 8.0 Hz, 1H), 7.76 (d, J=8.4 Hz, 1H).

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

To a stirred solution of **1** (1.13 g, 3.39 mmol) in ethanol(150 ml) at 0℃ was added sodium borohydride (128 mg, 3.39 mmol) by several portions. The solution was stirred at room temperature for 20min., cooled to 0℃, and acidified with 5% hydrochloric acid. The mixture was evaporated *in vacuo* to remove ethanol, 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 10% 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, 1H), 3.09-2.66 (m,4H), 3.82 (s, 3H), 4.8 (br s, 1H, D_2O exchangable), 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℃ 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 24hours 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′ tetramethyethylenediamine (2.29 ml, 15.2 mmol) in tetrahydrofuran (20 ml) at −78℃ under a nitrogen atmosphere was added n-butyllithium in hexane (9.48 ml, 15.2 mmol). The solution was stirred at −78℃ 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 (d, J=6.82 Hz, 3H), 1.93 (br s, 1H, D_2O exchangable), 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_2Cl_2-benzene (1 : 1, 10 ml) was added anhydrous *tert*-butyl hydroperoxide in toluene (3.3 M, 1.01 ml, 3.33 mmol). The solution was stirred at 0℃ for

2 h., and left in freezer for 10 h. The mixture was diluted with benzene, washed successively with 5% aqueous Na_2SO_3 solution, water, and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (eluted with 20% ethyl acetate in hexane) to afford 516 mg (84%) of *erythro*-**5** as a liquid: R_f=0.42 (33% ethyl acetate in hexane); IR(neat) 3450, 1220; ^{1}H-NMR (300 MHz, $CDCl_3$) 1.30 (d, J=6.3 Hz, 3H), 1.80 (ddd, J=14, 14, 5.7, 1H), 2.15 (dd, J=14, 6.2, 1H), 2.36-2.48 (m, 2H), 3.07 (dd, J=16.2, 5.7 Hz, 1H), 3.81 (s, 3H), 3.95 (s, 1H), 4.11 (q, J=6.3 Hz, 1H), 6.86 (d, J=8.1 Hz, 1H), 7.02 (d, J=7.5 Hz, 1H), 7.18 (dd, J=7.5, 8.1 Hz, 1H). Reversed phase HPLC analysis (ODS-C_{18}, 30% acetonitrile in water) of the crude product shows a small peak at 13.6 min. (3%), corresponding to the *threo*-**5**, and a large peak at 14.8 min. (97%), corresponding to the *erythro*-**5**. For the purpose of identification, the *threo*-**5** isomer was prepared by mcpba-epoxidation of **4**. *Threo*-**5**: R_f=0.35 (33% ethyl acetate in hexane); ^{1}H-NMR (300 MHz, $CDCl_3$) 1.35 (d, J=6.6 Hz, 3H), 1.65-1.76 (m, 1H), 2.3-2.43 (m, 2H), 3.04-3.11(m, 1H), 3.82 (s, 3H), 3.82(q, J=6.6, 1H), 3.87 (s, 1H), 6.86 (d, J=8.1 Hz, 1H), 7.01 (d, J=7.5Hz, 1H), 7.17 (dd, J=7.5, 8.1 Hz, 1H).

2-(1'-Hydroxyethyl)-5-methoxy-1,2,3,4-tetrahydro-2-naphthol (6)

To the epoxy alcohol **5** (560 mg, 2.5 mmol) in dry tetrahydrofuran (25 ml) was added lithium aluminium hydride (208 mg,5.5 mmol). The solution was stirred at room temperature for 15 hrs, and then the reaction was quenched by addition of water (0.5 ml). The mixture was diluted with ethyl acetate, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (eluted with 40% ethyl acetate in hexane) to afford 391 mg (70%) of **6** as a white solid: mp. 127-128℃ (recrystallized from hexane-ethyl acetate); IR (KBr) 3350; ^{1}H-NMR (80 MHz, $CDCl_3$) 1.22 (d, J=6.3 Hz, 3H), 1.5-2.0 (m, 2H), 2.06 (br s, 1H), 2.28 (br d, 1H), 2.77 (s, 2H), 3.70 (q, J=6.3 Hz, 1H), 3.81 (s, 3H), 6.68 (d, J=7.9 Hz, 1H), 6.69 (d, J=7.8 Hz, 1H), 7.11 (dd, J=7.8, 7.9 Hz, 1H).

5'-Methoxy-2,2,5-trimethyl-3',4'-dihydrospiro[1,3-dioxolane-4,2'(1'H)-naphthalene] (7)

To a mixture of the diol **6** (54 mg, 0.24 mmol) and p-toluenesulfonic acid (5 mg) in dry dichloromethane (5 ml) was added 2,2-dimethoxypropane (0.12 ml, 0.9 mmol). The solution was stirred at room temperature for 15 hrs, and then the reaction was quenched by addition of saturated sodium bicarbonate (0.5 ml). The mixture was diluted with dichloromethane, washed with water, and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (eluted with 2% ethyl acetate in hexane) to afford 42 mg (66%) of 7 as an oil: IR (neat) 3000, 1590; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 1.14 (d, J=6.1 Hz, 3H), 1.40 (s, 3H), 1.46 (s, 3H), 1.7-2.0 (m, 2H), 2.6-2.9 (m, 4H), 3.81 (s, 3H), 4.04 (q, J=6.1 Hz), 6.67 (d, J=7.9 Hz, 1H), 6.69 (d, J=7.8 Hz, 1H), 7.06 (d, J=7.9 Hz, 1H), 7.16 (d, J=7.8 Hz, 1H).

2-Hydroxymethyl-5-methoxy-3,4-dihydronaphthalene (8)

To a stirred solution of **3** (139 mg, 0.57 mmol) in tetrahydrofuran (20 ml) at −78℃ under a nitrogen atmosphere was added *tert*-butyllithium in hexane (1.7 M, 0.67 ml, 1.14 mmol). The solution was stirred at −78℃ for 20 min, and then paraformaldehyde(51.5 mg, 1.72 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 15% ethyl acetate in hexane) to afford 63 mg (30%) of **8** as a pale yellow liquid: IR (neat) 3300, 1645; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 1.60 (br s, 1H), 2.26 (t, J=8.2 Hz, 2H), 2.85 (t, J=8.2 Hz, 2H), 3.82 (s, 3H), 4.22 (br s, 2H), 6.41 (br s, 1H), 6.69 (d, J=7.6 Hz, 1H), 6.73 (d, J=7.7 Hz, 1H), 7.12 (dd, J=7.7, 7.6 Hz, 1H)

1,2-Epoxy-2-hydroxymethyl-5-methoxy-1,2,3,4-tetrahydronaphthalene (9)

To the allylic alcohol **8** (259 mg, 1.38 mmol) in dry dichloromethane (20 ml) was added *m*-chloroperbenzoic acid (70%, 483 mg, 1.96 mmol) by several portions at 0℃. The solution was stirred at room temperature for 60 min., and then the reaction was quenched by addition of saturated sodium bisulfite solution (1 ml). The mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate, water, and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (eluted with 20% ethyl acetate in hexane) to afford 279 mg (98%) of **9** as a pale yellow liquid: IR (neat) 3400; ^{1}H-NMR (80 MHz, $CDCl_3$) 2.3-1.8 (m, 2H), 2.6-2.3 (m, 3H), 3.2-2.9 (m, 1H), 3.81 (s, 3H), 3.93 (br s, 2H), 7.3-6.8 (m, 3H).

1,2-Epoxy-2-tert-butyldimethylsilyoxymethyl-5-methoxy-1,2,3,4-tetrahydronaphthalene (10)

To the epoxy alcohol **9** (113 mg, 0.55 mmol) in dimethylformamide (2 ml) at 0 ℃ was added imida-

zole (80 mg, 1.32 mmol) and *tert*-butyldimethysilyl chloride. The mixture was stirred at room temperature for 24 h, diluted with hexane (50 ml), washed with water, and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (eluted with 5% ethyl acetate in hexane) to afford 147 mg (94%) of **10** as a liquid: IR (neat) 2900, 1590, 1270, 1100; ^{1}H-NMR (80 MHz, $CDCl_3$) 0.10 (s, 6H), 0.93 (s, 9H), 1.7 (m, 2H), 2.3 (m, 2H), 3.77 (s, 1H), 3.81 (s, 3H), 3.89 (s, 2H), 7.3-6.7 (m, 3H).

2-Hydroxymethyl-5-methoxy-1,2,3,4-tetrahydro-2-naphthol (11)

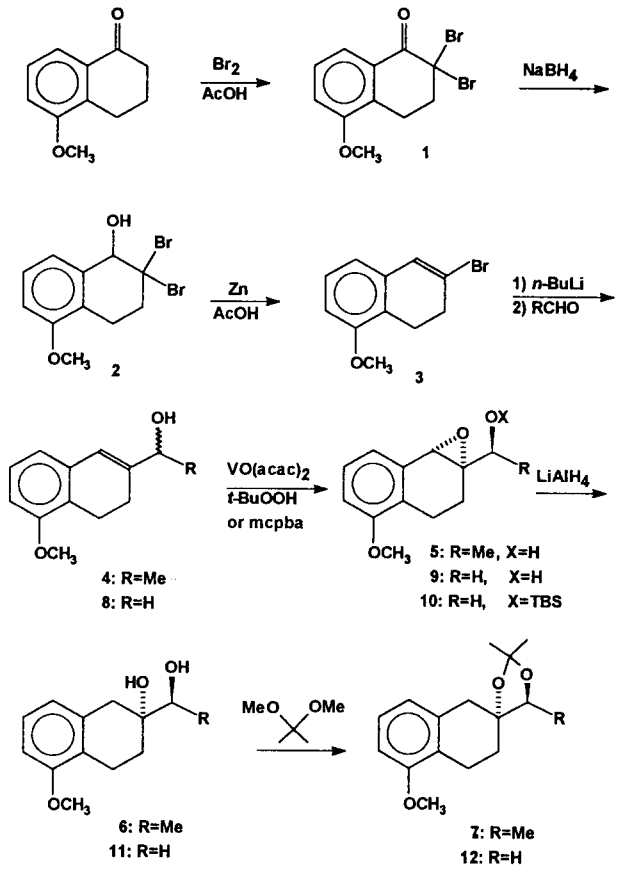
To the epoxide **10** (46 mg, 0.16 mmol) in dry tetrahydrofuran (5 ml) was added lithium aluminium hydride (20 mg, 0.5 mmol). The solution was refluxed for 4 days, cooled to room temperature, and the reaction was quenched by addition of water (0.2 ml). The mixture was diluted with ethyl acetate, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (eluted with 25% hexane in ethyl acetate) to afford 34 mg (100%) of **6** as a white solid: IR (KBr) 3350, 3000, 2950, 1580, 1255, 1100; ^{1}H NMR (80 MHz, $CDCl_3$) 1.86-1.69 (m, 2H), 2.20 (br s, 2H), 2.82-2.69 (m, 2H), 3.52 (br s, 1H), 3.57 (br s, 1H), 3.81 (s, 3H), 6.68 (d, J=7.8 Hz, 1H), 6.68 (d, J=7.8 Hz, 1H), 7.11 (dd, J=7.8, 7.8 Hz, 1H).

5'-Methoxy-2,2,-dimethyl-3',4'-dihydrospiro[1,3-dioxolane-4,2'a5(1'H)-naphthalene] (12)

To a mixture of the diol **11** (100 mg, 0.48 mmol) and p-toluenesulfonic acid (5 mg) in dry dimethylformamide (5 ml) was added 2,2-dimethoxypropane (0.4 ml, 3.26 mmol). The solution was stirred at room temperature for 15 hrs, and then the reaction was quenched by addition of saturated sodium bicarbonate (0.5 ml). The mixture was 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 2% ethyl acetate in hexane) to afford 116 mg (98%) of **12** as an oil: IR(neat) 3000, 1590; ^{1}H-NMR (80 MHz, $CDCl_3$) 1.45 (s, 6H), 1.8-2.0 (m, 2H), 2.6-2.9 (m, 4H), 3.81 (br s, 5H), 6.67 (d, J=7.7 Hz, 1H), 6.67 (d, J=7.7 Hz, 1H), 7.06 (d, J=7.7 Hz, 1H), 7.16(d, J=7.7 Hz, 1H).

RESULTS AND DISCUSSION

Efficient synthesis of anthracyclines requires the preparation of enantiomerically pure aglycones which include the asymmetric centers present on the A ring. Thus, construction of chiral AB synthons is a key step



Scheme 1

in the synthesis of anthracycline derivatives. Although some chiral AB synthons for anthracyclines were prepared by various methods (Holland and Viski, 1991), few chiral synthons for the 11-deoxy compound have been prepared (Hauser and Tommasi, 1991; Sekizaki *et al.*, 1982). Among the asymmetric syntheses developed to date, Sharpless asymmetric epoxidation is known as one of the most efficient methods for the preparation of chiral compounds. Our approach, outlined in Scheme 1, demonstrates an efficient synthetic route to the racemic AB synthon (**7**, **12**) via prochiral (**8**) or racemic allylic alcohol (**4**) derivatives which, in turn, can be readily transformed into chiral diols by application of Sharpless asymmetric epoxidation (Dominguez and Cava, 1983; Izawa *et al.*, 1987; Rao *et al.*, 1984; Sodeoka *et al.*, 1985). We choose 5-methoxy-1-tetralone as a starting material for the efficient introduction of A ring functionality. However, because of the highly enolizable carbonyl group of the tetralone starting materials, our initial attempts to introduce the side chain at the position α to the carbonyl group by enolate chemistry were greatly hampered by concomitant formation of o-alkylated products. To take advantage of this propensity, direct dibromination of 5-methoxy-1-tetralone can be effected with bromine in acetic acid in 99% yield. Subsequent reduction and

reductive elimination of the dibromide **1** afforded the vinyl bromide **3** in 80% yield. These overall steps are carried out under relatively mild reaction conditions such that large scale synthesis is possible. In addition, the vinyl bromide is a versatile intermediate for the elaboration of the A ring side chain. After being converted to the vinyl lithium or transition metal complex, it could be reacted with a variety of electrophiles and nucleophiles. In this work, the vinyl bromide was converted to the corresponding vinyl lithium by halogen-metal exchange, then reacted with acetaldehyde and paraformaldehyde to afford the allylic alcohols **4** and **8**, respectively. Subsequent epoxidation of 4 by *meta*-chloroperbenzoic acid (MCPBA) provided the epoxy alcohol **5** in good yield, but without any selectivity. We obtained a 1 : 1 mixture of both diastereomers. The ^{1}H-nuclear magnetic resonance (NMR) spectrums of the less polar compound on silica-precoated thin layer chromatography (TLC) exhibited the epoxide proton (C_1) as a singlet at 3.95 ppm. The corresponding resonance for the more polar diastereomer was observed at 3.87 ppm. However, because these peaks slightly overlapped with the methoxy peak (3.82 ppm) at C_5, we could not determine the exact diastereomeric ratio of products by NMR analysis. Thus, the ratios were determined by C_{18}-reversed phase high performance liquid chromatography (30% acetonitrile in water). Highly diastereo-selective epoxidation of **4** could be achieved with *tert*-BuOOH/VO(acac)$_2$, giving a 97 : 3 mixture of *erythro*-**5** with higher R_f value on TLC and *threo*-**5** with lower R_f value. The relative configuration of epoxy alcohol **5** was not rigorously established at this stage but was assigned tentatively on the basis of Sharpless's mnemonic. In general, Sharpless asymmetric epoxidation or vanadium-catalyzed epoxidation of allylic alcohols having a similar structure to that of **4** were reported to show a high *erythro*-selectivity (Dominguez and Cava, 1983; Martin *et al.*, 1981; Mihelich, 1979; Rossiter *et al.*, 1979; Sharpless and Michaelson, 1973; Tanaka *et al.*, 1974; Terashima and Tanno, 1983; Yasuda *et al.*, 1979). Considering the proposed reaction mechanism of catalytic epoxidation (Chong and Sharpless, 1977; Sharpless and Verhoeven, 1979; Itoh *et al.*, 1979; Mihelich, 1979; Rossiter *et al.*, 1979), the two conformers (I and II) shown in Fig. 2 might afford *erythro*-**5** and *threo*-**5**, respectively. Since steric interaction between the C_3-methylene and the (1'-hydroxy) ethyl group is clearly smaller in I than II, the conformer (I) should predominate in the epoxidation, resulting in the preferential formation of *erythro*-**5** (Terashima and Tanno, 1983). In addition, our preliminary result also reveal that the optically active *erythro*-epoxy alcohol **5** was formed exclusively by the Sharpless asymmetric epoxidation of **4** using L-(+)-tartrate and Ti(O-i-Pr)$_4$. Regiospecific epoxide ring opening of **5** can be achieved by lithium aluminium hydride

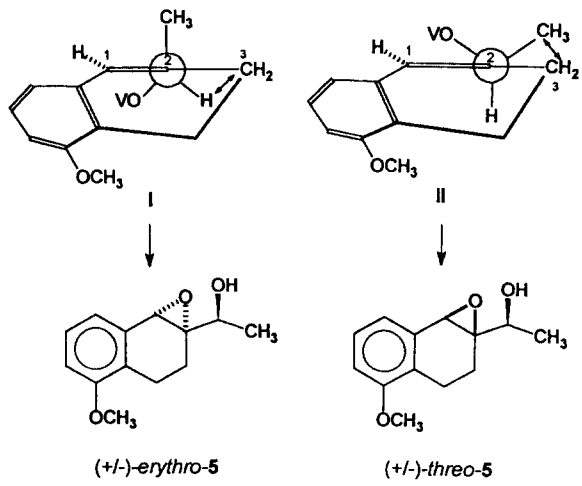


Fig. 2.

(LAH) to give diol **6** in 70% yield. On the other hand, direct ring opening of **9** with LAH produced both regioisomers. Formation of the unwanted regioisomer seems to be the result of intramolecular hydride attack at the more substituted side of epoxide through the chelated complex of the alcohol and LAH. Therefore, we protected the hydroxyl function of epoxy alcohol **9** as the *tert*-butyldimethylsilyl ether prior to reduction. Then, treatment of epoxide **10** with LAH gave us diol **11** directly, which presumably arises from regioselective hydride attack at the less hindered side of epoxide and concurrent desilylation. Both diol **6** and **11** were protected as acetonides to give **7** and **12**, respectively for further manipulation (Broadhurst and Hassall, 1982; Thomas, 1990).

In summary, we have shown that vinyl bromide **3** serves as a versatile and synthetically useful intermediate for allyic alcohols **4** and **8** which might be readily converted to chiral epoxy alcohols by application of Sharpless asymmetric epoxidation. Thus, this new and convenient method provide easy access to the syntheses of functionalized chiral 11-deoxyanthracycline derivatives.

ACKNOWLEDGMENT

This work was financially supported by the research grant from Research Center for New Drug Development in Korea.

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