A Facile Total Synthesis of Idarubicinone

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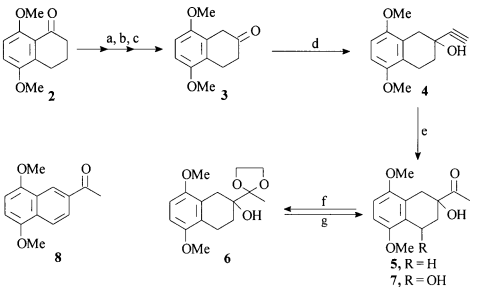
The anthracyclines of the daunomycinones (Figure 1) are important and clinically useful anticancer chemotherapeutic agents.[1] Adriamycin (**1a**),[2] daunorubicin (**1b**),[3] and carminomycin (**1c**)[4] are natural glycosides whose anti-cancer activity was demonstrated in the 1960-1970's. However, their therapeutic efficacy is limited due to a number of undesirable side effects. Epirubicin (**1d**)[5] and idarubicin (**1e**)[6] are totally synthetic analogues[7] that exhibit improved pharmacological profiles. In particular, **1e** is a promised antileukemic agent and shows activity in various tumor types also when given orally, whereas **1d** is replacing its epimer **1a** in a great number of polichemotherapy regimens because of its reduced cardiotoxicity.[8] The corresponding glycosides, **1a-1e** are examples[2-6] of daunomycins bearing an acetyl group at C-9 without any functional group at C-10 of the anthracycline framework. In more recent papers, we also published the synthesis of novel daunorubicinone derivatives.[9a,10a]

We now report a simple and convergent total synthesis of (+)-idarubicinone (**14**), the racemic aglycone of anticancer antibiotic idarubicin (**1e**). Our synthetic strategy employed is the Friedel-Crafts condensation[10] of AB-synthon **5** with phthaloyl chloride to give the tetracyclic skeleton. Additionally, we wish to describe a short synthesis of the AB-synthon necessary for the synthesis of the aglycone.

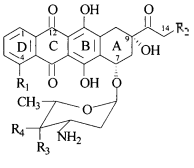
Results and Discussion

In the previous reports, we frequently used the Michael type reaction[9a-c] or the Friedel-Crafts acylation[10a] for the effective construction of tetracyclic skeleton in anthracyclinone. In this paper, we synthesized idarubicinone (**14**) using the Friedel-Crafts acylation of preformed bicyclic AB-ring synthon **5** with D-ring phthaloyl chloride (**9**). For this target, our AB-synthon was prepared from α-tetralone (**2**) by the sequence depicted in Scheme 1. α-Tetralone (**2**), which is prepared from 1,4-dimethoxybenzene and succinic anhydride *via* the Haworth synthesis,[11] was chosen as the starting material. Ethynylation of the C-2 carbonyl of β-tetralone (**3**) (which is readily obtained from α-tetralone (**2**) through four steps according to the reported procedure[12]) with lithium acetylide/ethylenediamine complex[13] in THF gave ethynyl carbinol **4** in 72% yield. 1-Ethanone **5** was prepared in 84% yield by treatment of carbinol **4** with yellow mercuric oxide (HgO)[14] and 20% aqueous sulfuric acid in THF followed by hydrolysis with 1N hydrochloric acid solution. We have also investigated the synthesis of the other synthon **7**. Protection of ketone **5** with ethylene glycol and catalytic amounts of *para*-toluenesulfonic acid (*p*-TsOH) in refluxing benzene[14] gave ketal **6** in 95% yield. Synthetic attempts of **7** through bromination[15] followed by hydrolysis under various reaction condition was not successful and naphthalene **8**[16] was mainly obtained accompanied by lesser amount of complex mixture, probably due to the aromatization of A-ring site by acidic condition. Therefore, we directly used 7-hydroxynaphthalenone **5** for the preparation of anthracyclinone framework.



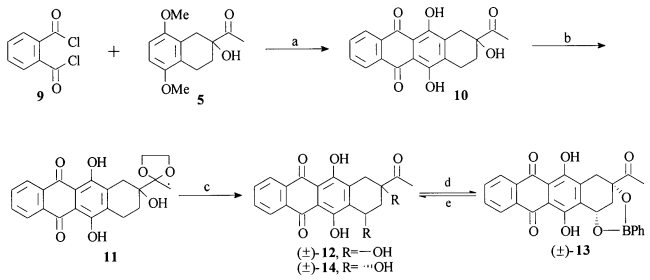
Scheme 1. (a) $NaBH_4$, 95% ethanol/H_2O. (b) *p*-TsOH, benzene, rfl. (c) i) OsO_4, trimethylamine N-oxide ii) *p*-TsOH, benzene, rfl. (d) Lithium acetylide/ethylenediamine complex, THF, rt. 18 h. (e) Yellow HgO, 20% H_2SO_4, THF, 1N HCl. (f) Ethylene glycol, *p*-TsOH · H_2O, benzene. (g) Br_2, AIBN, CCl_4, silica gel/wet THF, HCl/dioxane.

It had been previously established that phthaloyl chloride (**9**) could be condensed regiospecifically with some AB-ring moieties[10] in respectable yields. After condensation of **9** and **5** based on our work[10a] to afford **10** in 86% yield, protection of ketone **10** with ethylene glycol and catalytic amounts of *para*-toluenesulfonic acid in refluxing benzene[14] gave ketal **11** in 90% yield. Regiospecific bromination of **11** with bromine and azobisisobutyronitrile (AIBN) in refluxing carbon tetrachloride under irradiation with a 500 W halogen lamp[15] and solvolysis with silica gel in wet THF followed by deprotective hydrolysis with 1N HCl solution in dioxane gave mainly **12** in 53% yield. The selective *cis* diol protection of the products (**12**) with phenylboronic acid and *para*-toluenesulfonic acid in dry toluene[9a,b,10a,17] gave the benzene boronate (±)-**13** as a major product and trace amount of unidentified materials. After purification by column chromatography, the isolated *cis* boronate (±)-**13** was easily con-



1a. Adriamycin R_1 = OMe, R_2 = R_3 = OH, R_4 = H
1b. Daunorubicin R_1 = OMe, R_2 = R_4 = H, R_3 = OH
1c. Carminomycin R_1 = R_3 = OH, R_2 = R_4 = H
1d. Epirubicin R_1 = OMe, R_2 = R_4 = OH, R_3 = H
1e. Idarubicin R_1 = R_2 = R_4 = H, R_3 = OH

Figure 1



Scheme 2. (a) $AlCl_3$, nitrobenzene, rt. (b) Ethylene glycol, *p*-TsOH · H_2O, benzene. (c) Br_2, AIBN, CCl_4, silica gel/wet THF, HCl/dioxane. (d) $PhB(OH)_2$, *p*-TsOH/toluene, rt. (e) 2-Methyl-2,4-pentanediol, AcOH/CH_2Cl_2/acetone.

verted to *cis* diol (±)-**14** (82%) using 2-methyl-2,4-pentanediol in acetic acid. The NMR spectrum of the desired compound **14** exhibited scalar coupling patterns for *cis* form ($^3J_{7\text{-Heq},8\text{-Hax}}$ = 4.90 Hz, $^3J_{7\text{-Heq},8\text{-Heq}}$ = 1.98 Hz). The physical and spectral properties of this material were identical in all respects with the literature.[7]

Experimental Section

All reactions were run under dry nitrogen or argon atmosphere with oven-dried glassware. All solvents were purified according to literature procedure.[18] Bulk grade hexane was distilled prior to use. Merck pre-coated silica gel plates (Art. 5554) with fluorescent indicator were used as analytical TLC. Gravity column chromatography and flash column chromatography were carried out on silica gel (230-400 mesh from Merck) and HPLC was carried out on a Waters 4000 instrument having a Waters PDA UV spectrophotometer and a Waters 410 differential refractometer.

^{1}H NMR spectra were obtained on a JEOL JNM EX-400 spectrometer. Chemical shifts were internally referenced to TMS. Infrared spectra were recorded on a Nicolet 5-DXB series FT-IR spectrophotometer. Mass spectra were obtained on a JEOL JMX-DX 300 spectrometer by the electron impact or a Hewlett Packard 5972 series mass selective detector. Melting points were determined in capillary tubes on a Büchi 510 melting point apparatus and were uncorrected.

(±)-2-Ethynyl-2-hydroxy-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalene (4). A mixture of tetralone **3** (0.80 g, 3.88 mmol) and lithium acetylide/ethylenediamine complex (90%, 2.52 g, 27.15 mmol) was dissolved in dry tetrahydrofuran (100 mL) and stirred at room temperature for 18 hrs. The mixture was poured on ice water and extracted with ether. The combined ether extracts were washed with 5% sulfuric acid in the presence of crushed ice, then successively with saturated sodium hydrogencarbonate, water, brine, dried on anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel (benzene/ethylacetate – 20 : 1) and recrystallized from ether to give **4** (0.65 g, 72%) as a colorless solid with mp 103-105 °C. IR (KBr) cm^{-1} 3590 (OH), 3300, 1600, 1260 (OH); ^{1}H NMR (400 MHz, in $CDCl_3$) δ 6.64 (s, 2H, Ar), 3.75 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 2.68-3.09 (m, 4H, 2 × CH_2), 2.40 (s, 1H, CH), 2.24 (s, 1H, OH), 1.91-2.14 (m, 2H, CH_2); MS (m/z) 232 (M^+), 214 (M^+-H_2O).

(+)-2-Acetyl-2-hydroxy-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalene (5). A mixture of **4** (0.20 g, 0.86 mmol), yellow mercuric oxide (0.37 g, 1.72 mmol), and 20% sulfuric acid solution (4 mL) in dry tetrahydrofuran (50 mL) was heated at reflux for 5 hrs. After cooling, the mixture was diluted with 1N hydrochloric acid solution (20 mL) and extracted with methylene chloride. The combined organic layer was washed successively with distilled water, brine, dried on anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel (benzene/ethylacetate – 5 : 1) and recrystallized from chloroform/diethylether to give **5** (0.18 g, 84%) as colorless solid with mp 97-99 °C (lit.[13b] mp 100-101 °C). IR (KBr) cm^{-1} 3480 (OH), 1700 (C=O), 1492 (aromatic ring); ^{1}H NMR (400 MHz, in $CDCl_3$) δ 6.66 (s, 2H, Ar), 3.79 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.62 (s, 1H, OH), 2.75-3.01 (m, 4H, 2 × CH_2), 2.28 (s, 3H, CH_3), 1.83-2.05 (m, 2H, CH_2); MS (m/z) 250 (M^+), 232 (M^+-H_2O).

(+)-[1,1-(Ethylenedioxy)ethyl]-2-hydroxy-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalene (6). A mixture of **5** (2.30 g, 9.19 mmol), ethylene glycol (5.12 mL, 91.89 mmol), and *p*-toluenesulfonic acid monohydrate (0.14 g, 0.74 mmol) in benzene (100 mL) was heated at reflux for 2 hrs. The water generated during the reaction was azeotropically removed using a Dean-Stark apparatus. The cooled reaction was poured into aqueous sodium hydrogencarbonate, the benzene layer was separated and washed with brine and distilled water, then dried over magnesium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (hexane/ethylacetate – 4 : 1) and recrystallized from chloroform/diethylether to give **6** (2.57 g, 95%) as colorless solid with mp 114-116 °C. IR (KBr) cm^{-1} 3489 (OH), 2945, 1595 (aromatic ring), 1474, 1259 (OH), 1085 (C-O). ^{1}H NMR (400 MHz, in $CDCl_3$) δ 6.62 (s, 2H, ArH), 4.05 (s, 4H, 2 × CH_2), 3.78 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 2.71-2.89 (m, 2H, CH_2), 1.69-1.99 (m, 2H, CH_2), 1.43 (s, 3H, CH_3); ^{13}C NMR (100 MHz, in $CDCl_3$) δ 151.79, 150.95, 126.14, 124.33, 112.43, 106.82, 106.70, 74.34, 65.63, 65.55, 55.65, 55.51, 30.72, 27.11, 19.61, 19.43; MS (m/z) 294 (M^+), 261, 206, 189.

1-(5',8'-Dimethoxy-2'-naphthyl)-1-ethanone (8). A mixture of acetal **6** (0.73 g, 2.48 mmol), bromine (0.26 mL, 4.96 mmol), and catalytic amounts of azobisisobutyronitrile (8.14 mg, 0.05 mmol) in carbon tetrachloride (100 mL) was heated at reflux for 30 min with stirring under irradiation with a 500 W halogen lamp. After being cooled, silica gel (30 g, for column chromatography) and ice-cooled wet tetrahydrofuran (30 mL, containing about 3% water) were successively added to the mixture and stirred at room temperature for 2 hrs. Silica gel was separated by filtration and washed several times with methanol/dichloromethane (1 : 10). The combined organic layer was concentrated *in vacuo*. After the residue was dissolved in a mixture of 1N hydrochloric acid (15 mL) and dioxane (30 mL), the acidic solution was stirred

at room temperature for 20 hrs to hydrolyze the acetal group. The residue obtained by concentration of the mixture *in vacuo* was dissolved in chloroform. The organic solution was washed with brine, and distilled water, then dried on anhydrous magnesium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (hexane/ethylacetate = 4 : 1) to give **8** (0.31 g, 54%) as colorless solid with mp 110-112 °C. ^{1}H NMR (400 MHz, in $CDCl_3$) δ 8.65 (m, 1H, ArH), 8.26 (d, 1H, ArH), 8.03 (d, 1H, ArH), 6.99 (s, 1H, ArH), 6.72 (s, 1H, ArH), 4.00 (s, 3H, OCH_3), 3.99 (m, 3H, OCH_3), 2.74 (s, 3H, $COCH_3$); MS (m/z) 230 (M^+), 215 (M^+-CH_3), 189.

(±)-9-Acetyl-6,9,11-trihydroxy-7,8,9,10-tetrahydronaphthacen-5,12-dione, 7-deoxyidarubici-none (10). To a solution of **5** (0.45 g, 1.80 mmol) in nitrobenzene (20 mL) was added a solution of aluminum chloride (0.49 g, 3.65 mmol) in nitrobenzene (20 mL) at 0 °C and the mixture was slowly warmed to room temperature for 30 min. Phthaloyl dichloride (**9**) (0.28 mL, 1.98 mmol) was added to the resulting solution and the mixture was stirred at 100 °C for 1 hr. A solution of 0.2 N oxalic acid (30 mL) and ethylacetate (50 mL) were added to the resulting solution and filtered. The water layer was extracted with ethylacetate and the combined organic layer was washed with saturated sodium hydrogencarbonate and brine. After drying over anhydrous magnesium sulfate, the solvent was removed *in vacuo* and the crude material was purified by flash column chromatography (benzene/dichloromethane = 1 : 3) to afford **10** (0.54 g, 86%) with mp 217-219 °C. IR (KBr) cm^{-1} 3390 (OH), 1700 (C=O), 1618 (quinone), 1586 (aromatic rings), 1265 (OH); ^{1}H NMR (400 MHz, in $CDCl_3$) δ 13.48 (s, 2H, ArOH), 8.48-8.19 (m, 2H, Ar), 7.95-7.74 (m, 2H, Ar), 3.79 (bs, 1H, OH), 3.48-2.79 (m, 4H, CH_2), 2.39 (s, 3H, OCH_3), 2.19-1.68 (m, 2H, CH_2); MS (m/z) 352 (M^+), 309 (M^+-$COCH_3$).

(±)-[1,1-(Ethylenedioxy)ethyl]-6,9,11-trihydroxy-7,8,9,10-tetrahydronaphthacen-5,12-dione, (11). To a solution of **10** (0.11 g, 0.31 mmol), ethylene glycol (0.17 mL, 3.12 mmol), and *p*-toluenesulfonic acid monohydrate (8.31 mg, 0.04 mmol) in benzene was heated at reflux for 9 hrs, using a Dean-Stark appratus to remove the separated water. After cooling, the mixture was partitioned between dichloromethane and saturated aqueous sodium hydrogencarbonate and the organic layer was separated. The aqueous layer was extracted with dichloromethane and the combined organic layer was washed with brine, then dried over magnesium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (hexane/ethylacetate = 4 : 1) and recrystallization of this material from chloroform/diethylether afforded the pure acetal as pale yellow needles (0.11 g, 90%) with mp 202-204 °C. IR (KBr) cm^{-1} 3420 (OH), 1670 (quinone), 1590, 1550 (aromatic rings); ^{1}H NMR (400 MHz, in $CDCl_3$) δ 13.4 (s, 1H, ArOH), 13.1 (s, 1H, ArOH), 8.33-8.36 (m, 2H, ArH), 7.26-7.83 (m, 2H, ArH), 4.08 (s, 4H, $2 \times OCH_2$), 3.02-3.07 (m, 2H, CH_2), 2.84-2.88 (m, 2H, CH_2), 2.06-1.76 (m, 2H, CH_2); MS (m/z) 396 (M^-).

(±)-9-Acetyl-6,7,9,11-tetrahydroxy-7,8,9,10-tetrahydronaphthacen-5,12-dione, Idarubicinone (14). A) **12** from **11**: A mixture of acetal **11** (0.73 g, 1.84 mmol), bromine (0.19 mL, 3.68 mmol), and catalytic amounts of AIBN (6.05 mg, 0.04 mmol) in carbon tetrachloride (100 mL) was heated at reflux for 30 min with stirring under irradiation with a 500 W halogen lamp. After being cooled, silica gel (30 g, for column chromatography) and ice-cooled wet tetrahydrofuran (30 mL, containing about 3% water) were successively added to the mixture and stirred at room temperature for 2 hrs. Silica gel was separated by filtration and washed several times with methanol/dichloromethane (1 : 10). The combined organic layer was concentrated *in vacuo*. After the residue was dissolved in a mixture of 1N hydrochloric acid (15 mL) and dioxane (30 mL), the acidic solution was stirred at room temperature for 20 hrs to hydrolyze the acetal group. The residue obtained by concentration of the mixture *in vacuo* was dissolved in chloroform. The organic solution was washed with brine, and distilled water, then dried on anhydrous magnesium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (hexane/ethylacetate = 3 : 1) and recrystallized from chloroform/diethylether to give **12** (0.36 g, 53%).

B) *cis*-isomer **14** *via* **13**: A mixture of **12** (0.10 g, 0.27 mmol), phenylboronic acid (40.0 mg, 0.33 mmol) and *p*-toluenesulfonic acid (10.0 mg) in dry toluene (50 mL) was stirred at room temperature for 5 h. The reaction mixture was quenched with saturated aqueous sodium hydrogencarbonate and extracted with dichloromethane. The extract was washed with distilled water, dried on anhydrous magnesium sulfate, and concentrated *in vacuo* to give crude **13**. The residue was chromatographed on silica gel (hexane/ethylacetate = 4 : 1) to give pure **13** as red crystals.

A mixture of **13** (92.0 mg, 0.25 mmol), 2-methyl-2,4-pentanediol (0.32 mL, 2.50 mmol), acetic acid (20 L), dichloromethane (10 mL) and acetone (10 mL) was stirred at room temperature for 9 hrs. The reaction mixture was poured into a mixture of dichloromethane (20 mL) and saturated aqueous sodium hydrogencarbonate (20 mL). The organic layer was separated, washed with water, dried on anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash chromatography on a silica gel (dichloromethane/ethylacetate, 1 : 9 → dichloromethane/ethylacetate, 1 : 4), and by HPLC with a prep pak column (buffer solution, acetonitrile 35%; 0.02 M NaH_2PO_4 65%; triethylamine 0.1%; flow rate, 10 mL/min) to give 81.0 mg (81.5%) of *cis*-diol **14** as a dark yellow powder, mp 182.5-184 °C (lit.[6] mp 184-186 °C; lit.[7]; lit.[13c] mp 813.5-814.5 °C); IR (KBr) cm^{-1} 3332 (OH), 1720 (C=O), 1618 (quinone), 1584 (aromatic rings); ^{1}H NMR (400 MHz, in $CDCl_3$-DMSO-d_6) δ 13.58 (s, 1H, ArOH), 13.32 (s, 1H, ArOH), 8.41-8.27 (m, 2H, ArH), 7.92-7.78 (m, 2H, ArH), 5.56 (s, 1H, OH), 5.25 (m, 1H, CH), 4.88 (d, 1H, J = 7.0 Hz, OH), 3.20 (dd, 1H, $J_{10\text{-eq},10\text{-ax}}$ = 19.5 Hz, $J_{10\text{eq},8\text{eq}}$ = 1.98 Hz), 2.98 (d, 1H, J = 19.5, 10-H_{ax}), 2.43 (s, 3H, Ac), 2.36 (dt, 1H, $J_{8\text{-ax},8\text{-eq}}$ = 14.0 Hz, $J_{8\text{-eq},10\text{-eq}}$ = 1.98 Hz, $J_{8\text{-eq},7\text{eq}}$ = 1.98 Hz, 8-H_{eq}), and 2.06 (dd, 1H, $J_{8\text{-eq},8\text{-ax}}$ = 14.0 Hz, $J_{7\text{-eq},8\text{-ax}}$ = 4.90 Hz, 8-H_{ax}); MS (m/z) 368 (M^-).

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