Total Synthesis of a New 7-Deoxyidarubicinone Derivative through the Functionalization of an A-Ring Side Chain

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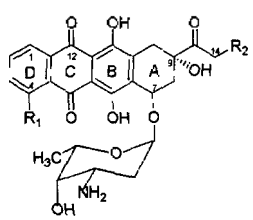
A convenient total synthesis of a new 7-deoxyidarubicinone derivative **21**, the aglycon of the anticancer antibiotic idarubicin analogue, is described. Key features of the synthesis are the Friedel-Crafts acylation and the functionalization of an A-ring side chain. A synthon **14** for the A and B rings was prepared from intermediate **6** in five steps.

Introduction

The clinical utility of the anthracycline antitumor antibiotics[1,2,3] such as doxorubicin (adriamycin) **1**, daunorubicin (daunomycin) **2**, and carminomycin **3** is well established (Figure 1). However, their uses for cancer chemotherapy are seriously hampered by their side effects, especially by dose-related cardiotoxicity. Therefore, numerous synthetic efforts have been devoted to overcome these disadvantages culminating in the development of artificial 4-demethoxyadriamycin **4** and 4-demethoxydaunorubicin (idarubicin) **5**, which could show improved pharmacological profile.[1-4] Since the biological activity of the anthracyclines is critically dependent on the functional groups at C-4, C-8, C-9, C-10, or C-14 positions in an aglycon, extensive efforts have been devoted to functionalization of these positions. Some anthracycline derivatives possessing fluorine atom or amine functions, the most interesting and promising congeners in light of the structure-activity relationship[5] have been synthesized recently.[6,7,8b,8c] In more recent papers, we have also reported the successful synthesis of various anthracycline derivatives.[8a-8e]

Herein, we describe the total synthesis of a new 7-deoxyidarubicinone derivative **21**, a potential prodrug[9] of anthracyclinone including an ester linkage of 14-OH in idarubicinone with a butyric acid residue. Additionally, we wish to des- cribe the synthetic studies on an AB-synthon **14** necessary for the synthesis of the aglycon.

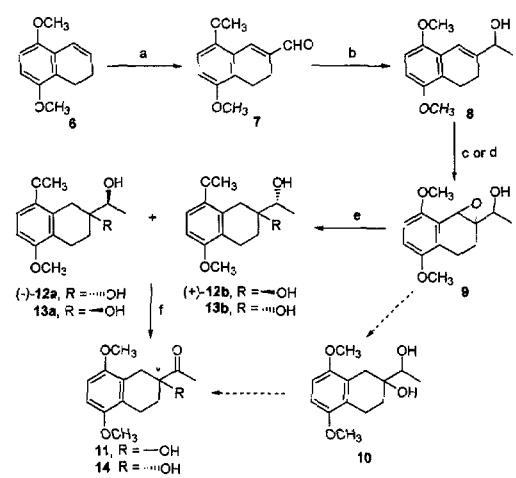


1, Adriamycin R_1 = OMe, R_2 = OH
2, Daunorubicin R_1 = OMe, R_2 = H
3, Carminomycin R_1 = R_2 = OH
4, 4-Demethoxyadriamycin R_1 = H, R_2 = OH
5, Idarubicin R_1 = R_2 = H

Figure 1. Some Daunomycin Derivatives.

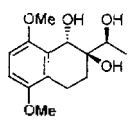
Results and Discussion

In the previous reports, we frequently used the Michael type reaction or the Friedel-Crafts acylation for the effective construction of tetracyclic skeleton in anthracyclinone.[8] In this paper, we synthesized a new 7-deoxyidarubicinone derivative **21** through the Friedel-Crafts acylation[8a,8c,16] of the preformed bicyclic AB-ring synthon **14** with D-ring phthaloyl dichloride (**17**) and the functionalization of C-14 site in the aglycon. For this target, our AB-synthon **14** was prepared from tetralene (**6**) by the sequence depicted in scheme 1. Tetralene (**6**) was obtained from tetralone by the known procedure.[10] Dasgupta and Ghatak reported the synthesis of α,β-unsaturated aldehyde **7** from a tetralone through three steps involving β-ketoacetals.[11] But, we synthesized the aldehyde **7** from tetralene **6** using Vilsmeier-Haack reagent[12] in one step. The Grignard reaction of aldehyde **7** with methylmagnesium bromide gave the addition product **8**. The double bond of **8** was subjected to epoxidation with various methods to produce epoxide **9**. Because the epoxide **9** were apt to be converted to undesired product when the material



Scheme 1. (a) $POCl_3$, DMF, 0 °C. (b) CH_3MgBr, THF, 10 °C. (c) *m*-CPBA, CH_2Cl_2, -10 °C. (d) Method A) *t*-BuOOH, $VO(acac)_2$, PhH, rt.; Method B) (+)-DIPT, $Ti(OiPr)_4$, *t*-BuOOH, CH_2Cl_2, -78 °C → 0 °C. (e) LAH, THF, rt. (f) Ag_2CO_3 on celite, PhH, reflux.

was handle with in an air atmosphere, the mixed product was directly used in the next reduction without separation. The first attempted method was applied by *m*-chloroperbenzoic acid (*m*-CPBA) mediated epoxidation which was previously reported.[8b,8d] The epoxidation of (±)-**8** using *m*-CPBA for the formation of racemate **11** was not successful and the unidentified materials and reactants were mainly recovered, probably due to the instability of the structure affected by the strong oxidant to prevent the desired intermediate. The second method involved the epoxidation with *tert*-butyl hydroperoxide and a catalytic amount of vanadium oxyacetylacetonate ($VO(acac)_2$) in benzene reported by Terashima *et al.*[13] The epoxidation of the racemic allylic alcohol (±)-**8** using Terashima method followed by reductive cleavage of the unstable epoxide (±)-**9** was found to give the intermediate (±)-**12/13** remaining some side products. The TLC spots were R_f = 0.75 (**8**), 0.5 (**12/13**), 0.3, and 0.27 (eluant: 50% ethylacetate in hexane). Therefore, we have also investigated to analyze the structure of the side products. Through a careful flash column chromatography using silica gel in hexane/ethylacetate as eluant, we could isolate diasteromeric mixture of (±)-**12/13** in 45% yield based on (±)-**8** and an isomer of the side compounds (**15/16**), which were much less than the desired products, in the ratio of about 1:5 determined by ^1H NMR analysis of the crude product. Direct recrystallization of the diasteromeric mixture of ((±)-**12/13**) in ether afforded the major diastereomer ((±)-**12**, 39%) in a pure state. The crude diasteromeric mixture ((±)-**12/13**) showed the two benzylic carbons as two strong signals at 29.1 and 30.7 ppm and two peak signals at 27.3 and 33.1 ppm in the ^{13}C NMR spectrum. The intergration ratio for the two sets of signals was found to be very similar to Terashima's results as 96 : 4. The last two compounds (R_f = 0.3 and 0.27) were also supposed to be diastereomers (2R*)-(**15/16**) having three hydroxyl groups based on the following spectroscopic and mass data: (a) two methine proton of **15** were observed at δ 5.45 (s, 1H) and 4.78-4.83 (q, 1H, J = 6.3 Hz, C-1'), whereas those of **16** were found at δ 5.08 (s, 1H) and 3.77-3.80 (q, 1H, J = 6.6, C-1'); (b) three hydroxyl protons of **15** or **16** were all disappeared when treating a few drop of D_2O; (c) the GC/MS spectrum showed at m/z 268 (M^+), 206, 191, 164, and 149. The formation of the isomer suggest that hydrolysis of unstable epoxide **12** occur in a moisture atmosphere. The last method was attempted under Sharpless condition using (+)-diisopropyl D-tartrate ((+)-DIPT), titanium (IV) isopropoxide ($Ti(OiPr)_4$), and *tert*-butyl hydroperoxide at -78 °C.[14] Optically pure (2R)-(−)-**12a** was obtained from **8** in 42% yield through the asymmetric epoxidation followed by reduction with lithium aluminum hydride. This method was always detected *ca.* 33% of unreacted material (**8**) due to the kinetic resolution, accompanied with small amounts of



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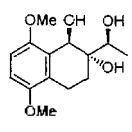

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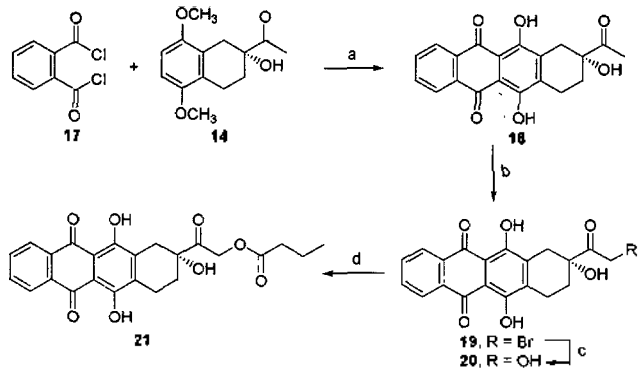

17 14 18 21

Scheme 2. (a) $AlCl_3$, $PhNO_2$, 80-100 °C. (b) PHT, THF, rt, 24 hrs. (c) 1% NaOH, Me_2CO, reflux. (d) $BuCO_2H$, DCC, DMF, rt.

side products as described above. Oxidation of (±)-**12** or (−)-**12a** with Fetizon reagent[15] in benzene afforded (±)-**11** and (−)-**14** in 90% and 78% yields, respectively. The physical and spectral properties of (±)-**11** or (−)-**14** were identical in all respects with the literature.[8a,13a-c,14a]

DA-125 containing a β-alanine residue developed by Dong-A Pharmaceutical Co., Ltd. (KR) was prepared by nucleophilic displacement coupling using a N-Boc-β-alanine sodium salt and a C-14 bromodaunomycin in acetone/water. The DA-125 prodrug was found to have higher anticancer activity and less cardiotoxicity than the previously reported daunorubicin family.[18] Therefore, we wish to also prepare a new anthracycline derivative through the functionalization of the C-14 position in a 7-deoxyidarubicinone. It had been previously established that phthaloyl chloride (**17**) could be condensed regiospecifically with some AB-ring moieties in respectable yields.[8a,8c,16] After condensation of **17** and (−)-**14** based on our published papers[8a,8c] to afford **18** in good yields, bromination of C-14 site with pyrrolidone hydrotribromide (PHT) in THF[17] gave **19** in 90% yield. Hydrolysis of **19** with 1% NaOH in refluxing acetone gave mainly **20** in 53% yield. The esterification[19] of the product **20** with butyric acid under dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in dry N,N'-dimethylformamide gave **21** (91%) as a major product and trace amount of unidentified materials. Since introduction of the 7-OH group in a 7-deoxyanthracyclinone has been reported previously in two steps,[8a-f] the developed route could provides aglycon of a new idarubicinone derivative.

Experimental Section

All reactions were run under dry nitrogen or argon atmosphere with oven-dried glassware, unless specified otherwise. All solvents were carefully dried and distilled by literature procedure[20] prior to use. 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).

^1H NMR and ^{13}C NMR spectra were recorded on a JEOL

JNM EX-400 spectrometer. Proton chemical shifts (δ) were reported in ppm downfield from tetramethylsilane (TMS), and ^{13}C resonance were recorded using the 77.0 ppm $CDCl_3$ resonance of the solvent as an internal reference and reported in ppm downfield from 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. Optical rotations were measured with JASCO DIP-360 spectrophotometer. Melting points were determined in capillary tubes on a Büchi 510 melting point apparatus and were uncorrected.

5,8-Dimethoxy-3,4-dihydro-2-naphthalencarbaldehyde (7). Phosphorus oxychloride (6.30 mL, 67.6 mmol) was added slowly to stirred dimethylformamide (20 mL) at 0 °C. The mixture was warmed to room temperature, stirred for 20 min, cooled to 0 °C, and added dropwise *via* a double-tipped needle into a solution of naphthalene **6**[10] (8.57 g, 45.0 mmol) in dimethylformamide (50 mL) at 0 °C. The ice bath was removed, and the orange reaction mixture was heated to reflux for 2-3 hrs. After cooling to 0 °C, a solution of sodium acetate (24.52 g, 0.18 mol) in water (80 mL) was added slowly. The mixture was refluxed for 30 min, cooled to room temperature, and extracted with diethyl ether (2 × 100 mL). The combined organic layers were washed with water, saturated aqueous sodium bicarbonate, and brine. After drying over anhydrous magnesium sulfate, the solution was concentrated to give **7** (7.17 g, 73%) as light yellow needles: mp 92-94 °C; ^1H-NMR ($CDCl_3$) δ 9.76 (s, 1H, CHO), 7.70 (s, 1H), 6.88 (d, J = 8.79 Hz, 1H, ArH), 6.76 (d, 1H, J = 8.79 Hz, ArH), 3.85 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.84 (t, 2H, J = 8.54 Hz, CH_2), 2.50 (t, 2H, J = 8.54 Hz, CH_2); ^{13}C-NMR ($CDCl_3$) δ 193.01, 150.92, 150.26, 140.36, 138.02, 127.43, 122.09, 113.86, 108.50, 56.05, 55.84, 20.01, 18.19; IR (film) 3052, 3005, 2952, 2824, 1655, 1481, 1252, 1085 cm^{-1}; MS (m/z) 218 (M^+), 189 (M-29), 174, 159, 144, 131, 115.

(±)-1-(5,8-Dimethoxy-3,4-dihydro-2-naphthalenyl)-1-ethanol (8). To a stirred solution of aldehyde **7** (8.97 g, 41.1 mmol) in tetrahydrofuran (100 mL) at 10 °C was added dropwise a solution of methylmagnesium bromide (20.5 mL, 61.6 mmol, 3.0 M in ether) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 hr. After completion of the reaction by monitored on TLC, saturated aqueous ammonium chloride was added and the mixture was extracted with ether (2 × 100 mL). The extracts were combined, dried over anhydrous magnesium sulfate, and evaporated. The residue was recrystallized from cyclohexane to give **8** as colorless needles (8.67 g, 90%): mp 78 °C; ^1H-NMR ($CDCl_3$) δ 1.34 (d, 3H, J = 6.35 Hz, CH_3), 2.25 (m, 2H, CH_2), 2.44 (s, 1H, OH), 2.76 (m, 2H, CH_2), 3.77 (s, 6H, $2OCH_3$), 4.42 (q, 1H, J = 3.4 Hz, CH), 6.68 (d, 1H, ArH), 6.64 (d, 1H, ArH), 6.77 (s, 1H, CH); ^{13}C-NMR ($CDCl_3$) δ 150.3, 149.4, 143.8, 124.5, 123.9, 115.3, 109.7, 108.5, 77.4, 56.0, 22.17, 21.5, 20.9; IR (film) 3402, 2938, 2838, 1474, 1252, 1098 cm^{-1}; MS (m/z) 234, 216 (M-18), 201, 175, 141, 128, 115.

1-(4,7-Dimethoxy-1a,2,3,7b-tetrahydronaphtho[1,2-*b*]oxiren-1-yl)-1-ethanol (9).

Attempted condition with (±)-8 and *m*-CPBA: A mixture of **8** (300 mg, 1.28 mmol) and *m*-CPBA (70%, 0.344 g, 1.54 mmol) was dissolved in 50 mL of methylene chloride and stirred at -10 °C for 2 hrs. The reaction mixture was diluted with 50 mL of methylene chloride and washed successively with 10% aqueous sodium carbonate solution and brine, dried over anhydrous sodium sulfate. This method was attempted under several different conditions. But, neither of these procedures was successful for the epoxidation, and only unidentified materials were mainly obtained.

(1S*)-1-[(1aR*,7bR*)-4,7-Dimethoxy-1a,2,3,7b-tetrahydronaphtho[1,2-*b*]oxiren-1-yl]-1-ethanol ((±)-9). *tert*-Butyl hydroperoxide (0.46 mL, 6.0 M solution in decane, 2.77 mmol) was added to a mixture of (±)-**8** (0.72 g, 3.07 mmol) and vanadium oxyacetylacetonate (0.11 g, 0.43 mmol) in benzene (100 mL), and the whole was stirred at room temperature for 45 min. Concentration *in vacuo* gave a crude mixture as a yellow oil. Because the resulting mixture was quite unstable, the mixed product was immediately used for the next reduction without further purification.

(1'S)-1-[(1aR,7bR)-4,7-Dimethoxy-1a,2,3,7b-tetrahydronaphtho[1,2-*b*]oxiren-1-yl]ethan-1-ol ((−)-9). (+)-Diisopropyl D-tartrate (89.8 μL, 0.43 mmol) was added at -75 °C to a solution of titanium (IV) isopropoxide (127.0 μL, 0.43 mmol) in methylene chloride (20 mL) under argon atmosphere. A solution of the olefin **8** (0.5 g, 2.13 mmol) in 10 mL of methylene chloride was then added, and the resulting mixture was stirred at -75 °C for 30 min. *tert*-Butyl hydroperoxide (356.0 μL of 6.0 M solution in decane, 2.13 mmol) was then added over a period of 15 min, and the reaction mixture was stirred at -75 °C for 1 hr, and allowed to reach 0 °C over a further period for 2 hrs. The organic solvent was concentrated by a rotavapor to give (−)-**9** as oil that could be used directly in the preparation of (−)-**12a** without further separation.

2-(1-Hydroxyethyl)-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthalenol ((±)-12) and Its Isomer ((±)-13) from (±)-9. A solution of above crude (±)-**9** (0.75 g, 3.01 mmol) in tetrahydrofuran (5 mL) was added dropwise to a suspension of lithium aluminum hydride (0.23 g, 6.06 mmol) in tetrahydrofuran (10 mL) at 0 °C and the whole was stirred at room temperature for 8 hrs. The reaction mixture was allowed to warm to room temperature before being cooled to 0 °C, quenched with 2N-sodium hydroxide (50 mL), and the upper organic phase was separated. The aqueous phase was further extracted with ethylacetate. The organic extracts were combined and washed successively with water and brine, and dried over magnesium sulfate. Filtration and concentration *in vacuo* gave a crude mixture of two pair of diastereomers (**12/13**, **15/16**), which was purified by flash chromatography (hexane/ethylacetate = 2/1 → 1/1) to give **15** (*ca.* 3.6%), **16** (*ca.* 18.1%), and **12/13** (0.35 g, 45.2% from **8**) as a white powder. Since separation of the a diastereomeric mixture of (±)-**12/13** (mp 142-148 °C) was not carried out throughout purification, this sample should consist of the two diasteromers in the ratio of 96 : 4 determined by ^{13}C NMR analysis of two benzylic carbons. The ^{13}C NMR spec-

trum of this sample supported this assumption. ^{13}C NMR (in $CDCl_3$): 29.1 (C_1 or C_4), 30.7 (C_1 or C_4) for (±)-**12** and 27.3 (C_1 or C_4), 33.1 (C_4 or C_1) for (±)-**13** (this ratio of two sets of signals was 96 : 4). The remaining portion of the crystals (350 mg) was directly recrystallized from diethyl ether to give pure (±)-**12a** as white crystals (302 mg, 39%): mp 150-153 °C, (lit.[13b] 154-155 °C); ^1H-NMR ($CDCl_3$) δ 1.28 (d, 3H, J = 6.3 Hz, CH_3), 1.57-1.98 (m, 2H, CH_2), 2.59-2.54 (two s, 2H, OH), 2.70-3.00 (m, 4H), 3.72 (q, 1H, J = 6.3 Hz, methine H), 3.77 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 6.64 (s, 2H, ArH); ^{13}C-NMR ($CDCl_3$) δ 151.9, 151.3, 126.1, 124.2, 107.1, 72.8, 72.2, 55.6, 30.7, 29.1, 19.8, 17.1; IR (film) 3338, 2945, 1481, 1252, 1084 cm^{-1}; GC/MS (m/z) 252 (M^+), 234 (M^+-H_2O), 207 (100), 189 (38), 175.

(1S*,2R*)-2-[(1S*)-1-Hydroxyethyl]-5,8-dimethoxy-1,2,3,4-tetrahydro-1,2-naphthalenediol ((±)-15). Spectral data of (±)-**15**: ^1H-NMR ($CDCl_3$) δ 1.31 (d, 3H, J = 6.35 Hz, CH_3), 1.68-1.74 (m, 1H, CH), 1.80 (bs, 1H, OH), 2.08-2.15 (m, 1H, CH), 2.20 (bs, 1H, OH), 2.61-2.69 (m, 1H, CH), 2.96-3.01 (m, 1H, CH), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.78-4.83 (q, 1H, J = 6.35 Hz, methine H), 5.45 (s, 1H, methine H), 6.67 (d, 1H, J = 8.79, ArH), 6.78 (d, 1H, J = 8.79 Hz, ArH); GC/MS (m/z) 268 (M^+), 206 (100), 191, 180, 164, 149.

(1R*,2S*)-2-[(1S*)-1-Hydroxyethyl]-5,8-dimethoxy-1,2,3,4-tetrahydro-1,2-naphthalenediol ((±)-16). Spectral data of (±)-**16**: ^1H-NMR ($CDCl_3$) δ 1.30 (d, 3H, J = 6.35 Hz, CH_3), 1.64-1.71 (m, 1H, CH), 1.93-2.05 (m, 1H, CH), 2.55 (bs, 1H, OH), 2.71-2.89 (m, 2H, CH_2), 3.29 (bs, 1H, OH), 3.77-3.80 (q, 1H, J = 6.83 Hz methine H), 3.78 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.25 (bs, 1H, OH), 5.08 (s, 1H, methine H), 6.71 (s, 2H, ArH); GC/MS (m/z) 268 (M^+), 206 (100), 191, 180, 164, 149.

(2R)-2-((1'S)-1-Hydroxyethyl)-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthalenol ((−)-12a). Reaction of above unstable (−)-**9** and lithium aluminum hydride (20.0 mg, 0.53 mmol) in tetrahydrofuran (20 mL) as described for the preparation of (±)-**9** yielded unreacted **8** (0.17 g, *ca.* 33% recovered), (−)-**13** (0.23 g, 42% yield from **8**) as a pale yellow oil that crystallized on standing, mp 128-130 °C (white powder from ether/hexane), and small amounts of **15** and **16**. The compound (−)-**12a** had ^1H and ^{13}C NMR, IR, and mass data as reported above, $[\alpha]_D^{20}$ -36.7° (c = 0.9, CH_3OH), (lit.[13b] $[\alpha]_D$ -49.7° (c = 0.5, ethanol), lit.[14a] $[\alpha]_D$ -34.3° (c = 1.2)).

1-[2-Hydroxy-5,8-dimethoxy-1,2,3,4,-tetrahydro-2-naphthalenyl]-1-ethanone ((±)-11). Fetizon reagent (silver carbonate on celite 50 wt (%), 1.0 mmol of Ag_2CO_3 on 1.0 g of the reagent)[15] (8.52 g, 8.52 mmol) was added to a benzene solution (50 mL) of (±)-**12** (0.43 g, 1.70 mmol), and the mixture was heated at reflux for 30 min, then cooled. An insoluble material was filtered off and washed with benzene (50 mL). The combined filtrate and washings were concentrated *in vacuo*, giving brown oil. The residue was purified by flash chromatography (hexane/ethylacetate = 3/1) to give **11** (0.38 g, 90%) as colorless crystals: mp 100-102 °C; ^1H-NMR ($CDCl_3$) δ 1.83-2.05 (m, 2H, CH), 2.32 (s, 3H, CH_3), 2.75-2.99 (m, 4H), 3.62 (s, 1H, OH), 3.76 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 6.64 (d, 1H, J = 8.79 Hz, ArH), 6.67 (d, 1H, J = 8.79 Hz, ArH); IR (film) 3480, 1700, 1492 cm^{-1}; GC/MS (m/z) 250 (M^+), 232 (M^+-H_2O), 207 (100). Those spectral properties were identical with those reported.[8a,15a]

1-[(2R)-2-Hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthalenyl]-1-ethanone ((−)-14). Oxidation of (−)-**12a** (230 mg, 0.91 mmol) with Fetizon reagent[15] (3.64 g, 3.64 mmol) as described for the preparation of (±)-**11** yielded 177 mg (78%) of optically pure (-)-**14** after purification by crystallization in hexane: mp 128-130 °C; $[\alpha]_D^{20}$ -48.2° (c = 0.98, $CHCl_3$), (lit.[13b] mp 127-128.5 °C, $[\alpha]_D^{20}$ -49.7° (c = 0.5, ethanol), lit.[14a] 128-129 °C $[\alpha]_D^{20}$ -48.8° (c = 1.0, $CHCl_3$)). This sample exhibited the same spectral (IR, ^1H NMR, and mass data) properties[13b-c,14a] as described above.

(8R)-8-(2-Bromoacetyl)-6,8,11-trihydroxy-5,7,8,9,10,12-hexahydro-5,12-naphthacenedione (19). 7-Deoxyidarubicinone (−)-**18** ($[\alpha]_D^{20}$ -84.4° (c = 0.1, $CHCl_3$), 97%ee, lit.[13c] $[\alpha]_D^{20}$ -87.0° (c = 0.12, $CHCl_3$)) (0.35 g, 0.99 mmol) which was successfully obtained from previously reported papers[8a,8c] and pyrrolidone hydrotribromide (0.54 g, 1.09 mmol) were placed in tetrahydrofuran (50 mL) and stirred at 23 °C for 24 hrs. The reaction mixture was diluted with methylene chloride (50 mL), washed with water and brine, dried over anhydrous magnesium sulfate. The mixture was concentrated *in vacuo* to give red residue **19** (0.37 g, 86%): mp 170-171 °C; ^1H-NMR ($CDCl_3$) δ 13.44 (s, 2H, OH), 8.34 (m, 2H, ArH), 7.84 (m, 2H, ArH), 4.38 (s, 2H, CH_2), 2.86-3.25 (m, 4H, CH_2), 2.05-2.19 (m, 2H, CH_2); GC/MS (m/z) 431 (M^+), 413, 352.

(8R)-8-Glycoloyl-6,8,11-trihydroxy-5,7,8,9,10,12-hexahydro-5,12-naphthacenedione (20). A red residue **19** (0.30 g, 0.70 mmol) was dissolved in acetone (30 mL). After the acetone solution had been made alkaline (pH = 8) by the addition of 1% NaOH (1 mL), it was refluxed for 10 min and concentrated *in vacuo*. Water was added to the residue, and the aqueous mixture was extracted with methylene chloride, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford crude product as a solid. Flash column chromatography (hexane/ethylacetate = 1/1) afforded a pure **20** (0.21 g, 80%) as red powder: mp 192 °C; $[\alpha]_D^{20}$ +49.9° (c = 0.004, CH_3OH); ^1H-NMR (DMSO-d_5) δ 13.44 (s, 2H, OH), 8.34 (m, 2H, ArH), 7.72 (m, 2H, ArH), 4.75 (s, 2H, CH_2), 2.86-3.25 (m, 4H, 2 × CH_2), 2.05-2.19 (m, 2H, CH_2); IR (film) 3449, 2918, 2851, 1736, 1676, 1588, 1461, 1259, 1165, 1071 cm^{-1}; GC/MS (m/z) 368 (M^+), 350 (M^+-H_2O), 310, 292.

2-Oxo-2-[(2R)-2,5,12-trihydroxy-6,11-dioxo-1,2,3,4,6,11-hexahydro-2-naphthacenyl]ethyl butyrate (21). Dicyclohexylcarbodiimide (0.42 g, 2.04 mmol) was added to a solution of 7-deoxyidarubicinone **20** (0.25 g, 0.68 mmol), butyric acid (124.0 μL, 1.36 mmol), and catalytic amount of 4-dimethylaminopyridine (DMAP) (0.10 g, 0.81 mmol) in dry dimethylformamide (15 mL). The reaction mixture was allowed to stir at room temperature for 6 hrs. at which time the mixture was evaporated *in vacuo*. The residue was dissolved in methylene chloride (50 mL) and washed with water (80 mL) and brine (2 × 50 mL). After drying over magne-

sium sulfate, flash column chromatography (hexane/ethylacetate = 3/1) gave **21** (0.27 g, 90.6%) as a red solid: mp 169-170 °C; ^{1}H-NMR ($CDCl_3$) δ 13.48 (s, 2H, ArOH), 8.33-8.34 (m, 2H, ArH), 7.81-7.84 (m, 2H, ArH), 5.1 (s, 2H, CH_2), 2.9-3.6 (m, 4H, 2 × CH_2), 2.45 (t, 2H, J = 7.32 Hz, CH_2), 1.93-2.34 (m, 2H, CH_2), 1.63-1.83 (m, 2H, J = 7.32 Hz, 7.81 Hz, CH_2), 1.01 (t, 3H, J = 7.32 Hz, 7.81 Hz, CH_3); IR (film) 3429, 2925, 2858, 1723, 1635, 1582, 1467, 1273, 1085, 1017 cm^{-1}; GC/MS (m/z) 438 (M^+), 420 (M^+-H_2O), 368.

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