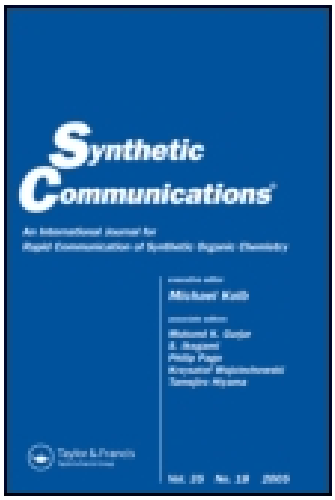

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Facile Total Syntheses of Idarubicinone-7-β-D-glucuronide: Convenient Preparations of AB-Ring Synthon Using Some Carboxylic Acid Derivatives

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Facile Total Syntheses of Idarubicinone-7-β-D-glucuronide: Convenient Preparations of AB-Ring Synthon Using Some Carboxylic Acid Derivatives

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ABSTRACT

Regiospecific syntheses of idarubicinone coupled with D-glucuronic acid are described. Cyclization of dimethoxybenzene with carboxylic acid derivatives in polyphosphoric acid (PPA) in one step afforded the naphthalenones **7**, which were transformed to the (±)-idarubicinone **3b** by general methods. Esterification of (±)-**3b** with (*S*)-(+)-*O*-acetylmandelic acid with subsequent separation and deprotection gave (+)-**3b** and (−)-**3b**. Reaction of separated two stereoisomers with acetobromo-α-D-glucuronic acid methyl ester respective followed by hydrolysis using lithium hydroxide and amberite cation exchange resin furnished

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two kinds of idarubicinone-7-β-D-glucuronide (**20** and **21**) that are coupled at C-7 position of idarubicinone.

Key Words: Anthracycline; Idarubicin analogs; Glucuronic acid; Glycosylation.

INTRODUCTION

Anthracycline antibiotics are well-known antitumor agents. Daunomycin (**1a**) and doxorubicin (**2a**) are a group of anthracyclines used widely in clinical therapy as a major drug in the treatment of solid tumors since the early 1970s. However, their utility is limited due to a number of side effects, the most series being dose-dependant cardiotoxicity.[1] Idarubicin (**3a**) or 4-demethoxydoxorubicin that belongs to one of the non-natural analogs was developed as artificial anthracyclines to improve the pharmacological profile (Fig. 1).[2] Its pharmacodynamic and pharmacokinetic properties published by Hollingshead and Faulds in 1991.[3] Because these compounds cannot be prepared from the fermentation process, there have been also a number of reports on the synthetic method of them. The antitumor activity of anthracyclines is mainly dependent on the chirality of A-ring, and they are active only in their natural absolute configuration.[4a] Therefore, much effort has been devoted to developing more efficient methods for the enantiomeric synthesis of aglycones.[4]

Recently, examples[5] are reports of coupling some drugs with glucuronide that were found to have enhanced drug efficacy. The syntheses of anthracycline analogs that are attached glucuronide at amino group of daunosamine in doxorubicin and/or daunomycin have been also reported.[6a] Studies comparing antitumor activities of these derivatives and corresponding anthracycline have been often reported.[6] However, the properties and preparation of idarubicinone-7-D-glucuronides that are coupled idarubicinone [(±)-**3b**]

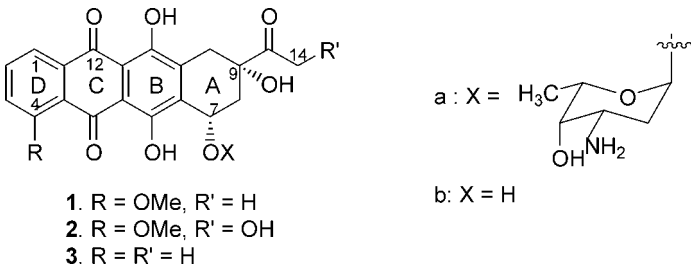

Figure 1. Some chemical structures of anthracyclines (**1**–**3**).

with D-glucuronic acid at C-7 have not been reported yet. In previous papers, we reported the syntheses of novel fucosyl anthracycline[7a] having a fluorine at C-9 position[7b] and idarubicinone (**3b**).[7c,d] Related to these reports, we wished to prepare some idarubicin analogs containing glucuronic acid.

In this paper, we wish to report the synthesis of new idarubicinone-7-β-D-glucuronide (**20** and **21**) attaching glucuronic acid moiety to (+)-**3b** and (−)-**3b**, respectively. Additionally, we wish to describe the facile synthetic method on an AB-ring synthon **7a**,**b** necessary for the synthesis of the aglycone.

RESULTS AND DISCUSSION

Many synthetic efforts have been devoted to prepare AB-synthon of idarubicinone (**3b**).[4] In this paper, we envisaged that Friedel–Crafts reaction using dimethoxybenzene would provide us with a naphthalenecarboxylic acid that could be readily converted to the desired synthon, which can then be built up to the tetracyclic ring system in gram scale. For this purpose commercially available starting materials, e.g., itaconic anhydride (**4**), itaconic acid (**5**), and 3-acetyl-3-butenoic acid (**6**) were considered as they can be formed into a mixture of **7** and **8** in one step (Sch. 1). The reaction of dimethoxybenzene with above carboxylic acid derivatives in the present of polyphosphoric acid (PPA) or $AlCl_3$ gave exciting results as follows: coupling dimethoxybenzene with itaconic anhydride (**4**) using PPA (100°C, 10 min)[8] gave the desired naphthalenecarboxylic acid **7a** and the undesired acrylic acid **8a** as 1 : 1 ratio in 82% yield (entry 1), whereas using $AlCl_3$ (1.2 eq, r.t., 4 hr/CH_2Cl_2) yielded as 1 to 4 ratio (**7a**/**8a**) in 83% yield (entry 2). However, the reaction of dimethoxylbenzene with itaconic acid (**5**) using PPA afforded **7a** and **8a** as 4 to 1 ratio in 82% yield because itaconic acid moiety strongly favors the cyclization reaction in PPA condition (entry 3), whereas using $AlCl_3$ produced no any product (entry 4). Moreover, the same reaction with 3-acetyl-3-butenoic acid (**6**) obtained from the known procedure[9] using PPA gave only **7b**[10] in 72% without producing **8b** (entry 5), whereas using $AlCl_3$ also furnished no any product (entry 6). Results of the coupling of dimethoxybenzene with some carboxylic acid derivatives are summarized in Table 1.

Tetralone **7a** can be transformed to **11** by appropriate reactions and the undesired **8** can be inverted to the desired **7** which can be recycled to **11**. Based on the prediction our attention has been directed to the preparation of **11**. **7a** for the synthesis of **11** was converted quantitatively into **9** with $NaBH_4$ (1.5 eq, 0°C, 2 hr/MeOH). But, when using excess $NaBH_4$, lactone **10**[11] was obtained in 85%. Reaction of **9** with methyl lithium (4.2 eq, 0°C, 2 hr/THF) for **9** transformed into **11** was not successful and only the lactone

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Scheme 1. Synthetic approach for the preparation of AB-ring synthon.

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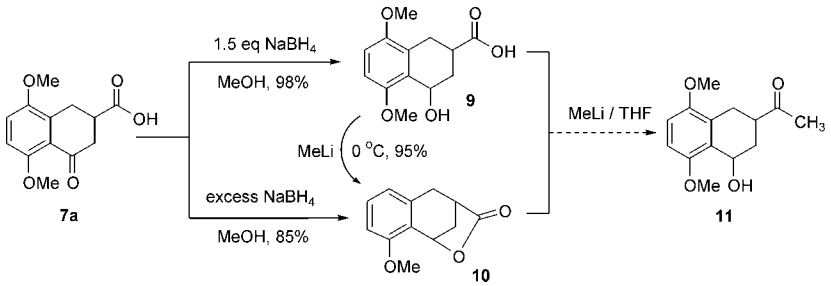
Table 1. Coupling of dimethoxybenzene with carboxylic acid derivatives (**4**, **5**, and **6**).

			Products	
Entry	Compound	Conditions	**7**/**8** (%)[a]	**7**/**8** ratio
1	**4**	PPA/100°C/10 min	**7a**(41)/**8a**(41)	50/50
2	**4**	$AlCl_3$/r.t./4 hr	**7a**(17)/**8a**(66)	20/80
3	**5**	PPA/100°C/10 min	**7a**(66)/**8a**(16)	80/20
4	**5**	$AlCl_3$/r.t./4 hr	—[b]	—
5	**6**	PPA/100°C/10 min	**7b**(72)/**8b**(0)	100/0
6	**6**	$AlCl_3$/r.t./4 hr	—[b]	—

[a]Isolated yield after SiO_2 column chromatography.
[b]Not obtained.

product **10** (94% overall yield) was mainly obtained because γ-hydroxy acids strongly favor the intramolecular lactonization rather than intermolecular nucleophilic attack by methyl lithium. Synthetic attempt for the formation of **11** from **10** using excess methyl lithium gave no reaction (Sch. 2). Moreover, the reduction of benzylic carbonyl group of **7b** using $NaBH_4$ or $NaBH_3CN$ to get **11** failed due to the non-selectivity of the reagents.

So, tetralin **13**[12] was obtained from **7a** by removing the carbonyl group with Et_3SiH/CF_3CO_2H followed by reacting with methyl lithium (3.5 eq, 0°C, 2 hr/THF) (Sch. 3). To introduce two hydroxy groups at C-2 and C-4, **13** was reacted under a basic oxygenation condition (O_2, −15°C, 4.2 eq *t*-BuOK, 2.2 eq $P(OEt)_3$/DMF).[13] However, monohydroxylated compound **14** was only obtained in 85%.[4c,8b] After protecting of carbonyl group of **13** using ethylene glycol or transformating two methoxy groups into hydroxy groups, the efforts to introduce hydroxy group at C-4 position failed. Therefore,



Scheme 2. Attempted methods for synthesis of **11**.

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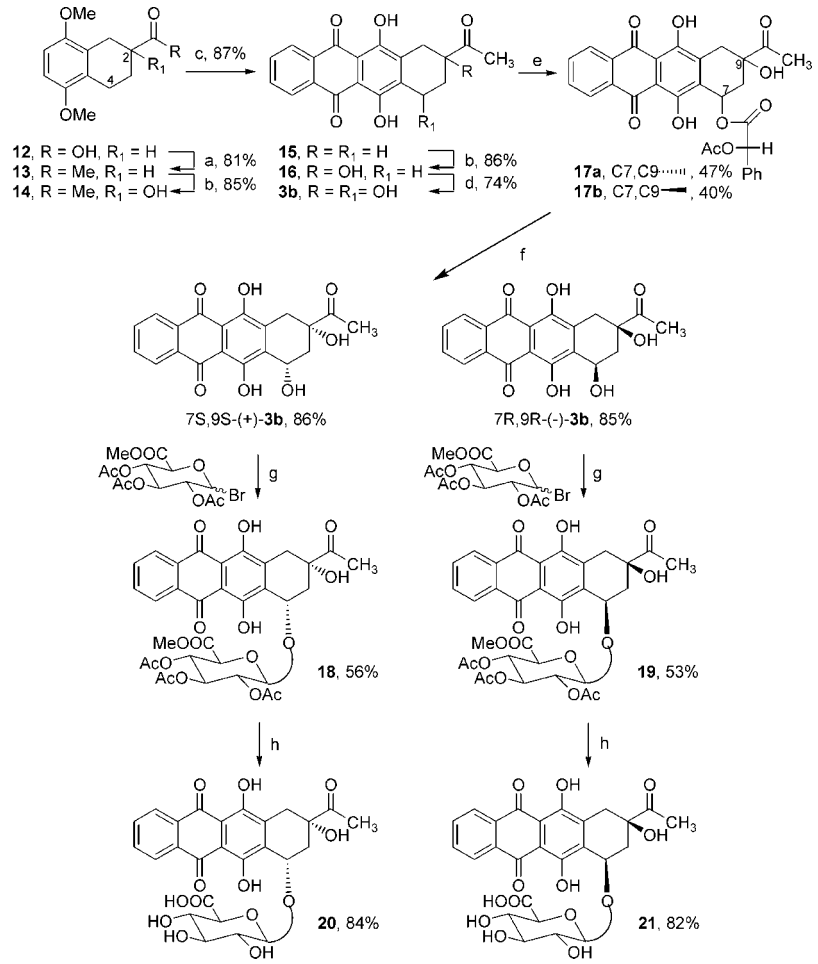

Scheme 3. (a) MeLi/THF, 0°C. (b) O_2, *t*-BuOK, $P(OEt)_3$/DMF, −15°C. (c) C_6H_4-1,2-$(COCl)_2$, $AlCl_3/PhNO_2$, 80–100°C. (d) 1. $HOCH_2CH_2OH$, *p*-TsOH/PhH, reflux. 2. NBS, AIBN/CCl_4, reflux; SiO_2/wet THF; HCl/dioxane. (e) (*S*)-(+)-*O*-Acetylmandelic acid, DCC, DMAP/CH_2Cl_2. (f) Satd. NaOH solution (5 drops). (g) $ZnBr_2$, 4 Å molecular sieves/CH_2Cl_2. (h) LiOH, Amberite resin/MeOH, THF.

7-deoxyidarubicinone (**16**) was made from direct condensation of phthaloyl dichloride with (±)-**14** without further chiral resolution.[14] Additionally, condensation of phthaloyl dichloride with **13** in the same manner yielding **15** (87%)[15] followed by treating **15** with the same basic oxygenation condition gave **16** in 86%[4c,8b,15a] without formation of product **3b**. Compound

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14 and **16** were observed as 1 : 1 ratio at 13.69 and 17.96 min and the same ratio at 43.32 and 53.47 min, respectively, by HPLC analysis (Daicel Chiralcel OD-H, 20% IPA in hexane, 0.5 mL min^{-1}, 254 nm, 20°C). And so, they should be racemic mixture. The esterification of (±)-**14** or (±)-**16** with resolving agents, (*S*)-(+)-*O*-acetylmandelic acid or (+)-tartaric acid for chiral resolution were not successful, probably due to steric hindrance from acetyl group and/or electron deficiency of hydroxy group resulting from electron withdrawing of carbonyl group. Therefore, we wished to isolate the racemate from diastereomer **3b** as follows: selective hydroxylation at C-7 position was achieved by converting carbonyl group at C-13 to acetal form using ethylene glycol and *p*-TsOH in refluxing benzene and preventing the introduction of OH group to C-14 and C-10 position. After bromination of the ketal with bromine and AIBN as a catalyst in refluxing CCl_4, cis form of **3b** as a major product was obtained in 78% by hydrolysis with silica gel in wet THF.[16] Racemate (±)-**3b** looked like one spot on TLC.[15a,17a] From HPLC analysis under the same manner above, however, it was confirmed that (±)-**3b** was 1 : 1 isomeric mixture at 85.64 and 103.12 min. After coupling OH group of C-7 in (±)-**3b** with (*S*)-(+)-*O*-acetylmandelic acid in the presence of DCC and DMAP in dichloromethane to afford compound **17a** and **17b** followed by isolation of two diastereomers by flash chromatography, cleavage the ester linkage with saturated NaOH produced the same isomers, optically active (+)-**3b** and (−)-**3b** in total 86%. The physical and spectral properties of obtained (+)-**3b** were identical in all respects with the literature.[4c,17b] However, the specific rotation of (+)-**3b** and (−)-**3b** were +159° (lit.[17b] $[\alpha]_D^{20}$ +154, c 0.1, dioxane) and −156° (c 0.1, dioxane), respectively. The retention time of two isomers were also 85.64 min for (−)-**3b** and 103.12 min for (+)-**3b** on HPLC spectra as described above. From NMR spectrum analysis, it was confirmed that two (±)-cis enantiomer **3b** were formed as axial forms from **16** as the results of Tamura and Kita.[16]

Glycosylation of acetobromo-α-D-glucuronic acid methyl ester prepared from glucuronolactone[5c,18] with (+)-**3b** or (−)-**3b** in the presence of $HgBr_2$ and HgO gave small amounts of desired β-anomers (**18** and **19**, ≤6%) accompanied by lesser amount of α-anomer and unidentical material. However, the attempt using $ZnBr_2$ gave only β-anomers, **18** (56%) and **19** (53%) through neighboring group participation of the Koenigs–Knorr reaction.[19] Their configurations were easily determined by analyzing scalar coupling constants[17,20,21] in NMR spectra of **18** and **19**. The 1′-H chemical shift of **18** and **19** were 5.16 ppm ($J_{1',2'} = 7.8$ Hz) and 5.05 ppm ($J_{1',2'} = 8.3$ Hz), respectively. The 2′-H of **18** and **19** was assigned to the double-doublet at 4.95 ppm and the observed coupling constants of 8.3 and 8.8 Hz, indicating the axial–axial interactions for both 1′-H and 3′-H protons on the sugar ring. Therefore, all products were β-configuration. The optical rotations of β-anomer were

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$[\alpha]_D^{20}$ $+45.5^\circ$ for **18** and -79.8° for **19**. Deprotection of the carbohydrate moieties of protected compounds (**18** and **19**) was carried out using 0.1 M lithium hydroxide and amberite cation exchange resin[5c,6a] to give idarubicinone-7-β-D-glucuronides, **20** (84%) and **21** (82%) which will be studied on biological activities.

In summary, we developed a synthetic method for the preparation of AB-ring synthon **14** using carboxylic acid derivatives. We also prepared ($\pm$)-idarubicinone (**3b**) from coupling phthaloyl dichloride with the AB-ring synthon **14** and isolated two isomers of (+)-**3b** and (−)-**3b** using (*S*)-(+)-*O*-acetylmandelic acid. Novel glycosides (**20** and **21**) containing glucuronic acid moiety were readily also prepared via glycosylation of (+)-idarubicinone **3b** and (−)-idarubicinone **3b** with acetobromo-α-D-glucuronic acid methyl ester using $ZnBr_2$, followed by hydrolysis with lithium hydroxide and amberite cation exchange resin. Detailed NMR analyses unambiguously proved the anomeric configuration of the new compounds.

EXPERIMENTAL SECTION

All the reactions were carried out under dry argon and nitrogen atmosphere with oven-dried glassware. 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 and ^{13}C NMR spectra were recorded on a JEOL JNM EX-400 spectrometer. Chemical shifts were internally referenced to TMS for ^{1}H or to solvent signals for ^{13}C. Infrared spectra were recorded on a Nicolet 5-DXB series FT-IR spectrophotometer. Mass spectra were obtained on a JEOL JNX-DX 300 spectrometer by the electron impact or a Hewlett Packard 5972 series mass selective detector and a JEOL JMS DX-110/110A Tandem mass spectrometer (FAB^+). UV-VIS absorption spectra were recorded on a Hitachi-556 spectrophotometer. The optical rotations were determined using the Rudolph AUTOPOL IV apparatus with a 0-100-1.5 polarimeter sample tube. Melting points were obtained on a Büchi 510 melting point apparatus and were uncorrected.

5,8-Dimethoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthalenecarboxylic acid (7a) and 2-[2-(2,5-dimethoxyphenyl)-2-oxoethyl]acrylic acid (8a). Method 1: Friedel–Crafts condensation. In a 100 mL three-necked, round-bottomed flask fitted with a magnetic stirrer and reflux condenser was placed itaconic anhydride (**4**) (0.61 g, 5.4 mmol) and dichloromethane (30 mL). After

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brief stirring, aluminum chloride (0.86 g, 6.5 mmol) was added all at once. The mixture was kept at room temperature for 10 min and added with 1,4-dimethoxybenzene (0.5 g, 3.6 mmol), and then stirred for 4 hr. The mixture was acidified with 2 N hydrochloric acid and then extracted with dichloromethane. The combined organic layer was washed with saturated sodium bicarbonate and brine. After drying over anhydrous magnesium sulfate, the solvent was removed in vacuo and the crude material was purified by flash column chromatography (ethyl acetate/hexane = 1 : 1) to afford **7a** (0.15 g, 17%) as a white solid and **8a** (0.60 g, 66%) as a pale yellow solid. **7a**: m.p. 180–182°C; ^{1}H NMR ($CDCl_3$) δ 7.03 (d, 1H, $J = 8.8$ Hz, ArH), 6.83 (d, 1H, $J = 8.8$ Hz, ArH), 3.87 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.41 (dd, 1H, $J = 17.09$, 3.42 Hz, $C_{1eq}H$), 3.16–3.09 (m, 1H, C_2H), 2.96 (dd, 2H, $J = 10.26$ Hz, C_3H), 2.85–2.78 (m, 1H, $C_{1ax}H$); ^{13}C NMR ($CDCl_3$) δ 194.21, 174.66, 149.70, 132.00, 116.54, 110.98, 56.08, 55.92, 41.80, 38.13, 30.70, 25.54; MS (m/z) 250 (M^+). **8a**: m.p. 106–118°C; ^{1}H NMR ($CDCl_3$) δ 7.36 (d, 1H, $J = 2.9$ Hz, 1H, ArH), 7.05 (dd, 1H, $J = 2.9$, 8.8 Hz, ArH), 6.45 (s, 1H, $=CH_2$), 5.73 (s, 1H, $=CH_2$), 4.01 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 197.78, 171.93, 153.43, 134.85, 129.92, 127.14, 120.88, 113.90, 113.07, 55.96, 55.77, 46.63; MS (m/z) 250 (M^+).

Method 2: Tandem acylation-cycloaddition. Itaconic acid (**5**) (1.31 g, 10.1 mmol) and 1,4-dimethoxybenzene (2.78 g, 20.1 mmol) were added to PPA (ca. 20 g), pre-heated to 100°C, and the mixture was stirred for 10 min before being cooled to room temperature. Water and concentrated aqueous NH_3 solution was added to the residue and the aqueous mixture was extracted several times with diethyl ether. The combined organic layer were dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo. The crude material was purified by flash column chromatography (ethyl acetate/hexane 1 : 1) to afford **7a** (3.32 g, 66%) as a white solid and **8a** (0.81 g, 16%) as a pale yellow solid. The physical and spectroscopic properties of the products agreed well with those of method 1.

3-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-1-naphthalenone (7b). Reaction of dimethoxybenzene (3.24 g, 23.4 mmol) and 3-acetyl-3-butenoic acid (**6**) (1.50 g, 11.7 mmol) in PPA (23.0 g) was carried out as described for the preparation of **7a** and **8a** (upper method 2) to give **7b** (4.19 g, 72%) as a white solid: m.p. 121–123°C (lit.[10] 120–122°C); IR (KBr) 1721, 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.02 (d, 1H, $J = 9.3$ Hz, ArH), 6.83 (d, 1H, $J = 8.8$ Hz, ArH), 3.86 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.36–3.31 (m, 1H, $C_{1eq}H$), 3.16–3.08 (m, 1H, C_2H), 2.84–2.80 (dd, $J = 11.7$, 4.4 Hz, 2H, C_3H), 2.77–2.71 (m, 1H, $C_{1ax}H$), 2.26 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 208.12, 195.90, 154.03, 150.17, 132.39, 122.32, 116.08, 110.51, 56.38, 56.08, 46.99, 41.81, 28.08, 25.41; MS (m/z) 248 (M^+).

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4-Hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthalenecarboxylic acid (9). To a stirred solution of ketone **7a** (2.0 g, 7.99 mmol) in methanol (20 mL) was added sodium borohydride (0.45 g, 12.0 mmol). The mixture was stirred for 2 hr at 0°C and quenched with acetone (10 mL). The solvents were removed in vacuo and then water and dichloromethane were added to the residue. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water, dried over anhydrous magnesium sulfate, and evaporated giving compound **9** (1.98 g, 98%) as a white crystal: m.p. 130–134°C; ^{1}H NMR ($CDCl_3$) δ 6.72 (s, 2H, ArH), 5.11–5.07 (m, 1H, C_4H), 3.86 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.09–3.04 (m, 1H, C_1H), 2.75–2.59 (d, 2H, C_3H), 2.52–2.47 (m, 1H, C_2H), 1.92–1.84 (m, 1H, C_3H); ^{13}C NMR ($CDCl_3$) δ 176.52, 151.30, 150.75, 127.70, 125.59, 108.43, 107.50, 65.51, 55.25, 55.22, 37.24, 32.76, 25.83; MS (m/z) 235 ($M^+ - OH$), 207 ($M^+ - COOH$).

3,6-Dimethoxy-11-oxatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-trien-10-one (10). Reaction of **7a** (2.40 g, 9.59 mmol) and excessive sodium borohydride (1.27 g, 33.6 mmol) in methanol (25 mL) was carried out as described for the preparation of **9** to give **10** as pale yellow crystal (1.66 g, 85%): m.p. 106–110°C; ^{1}H NMR ($CDCl_3$) δ 6.77 (d, 1H, $J = 8.8$ Hz, ArH), 5.92 (d, 1H, $J = 9.3$ Hz, ArH), 5.92 (d, 1H, $J = 5.4$ Hz, C_8H), 3.79 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.07–2.90 (m, 3H), 2.68 (qt, 1H, $J = 5.9$, 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 179.31, 151.66, 149.64, 126.01, 123.02, 110.93, 109.31, 71.77, 56.20, 55.52, 37.29, 33.93, 26.44; MS (m/z) 234 (M^+), 219 ($M^+ - CH_3$), 190 ($M^+ - COO$).

5,8-Dimethoxy-1,2,3,4-tetrahydro-2-naphthalenecarboxylic acid (12). A solution of ketone **7a** (0.39 g, 1.56 mmol) in trifluoroacetic acid (2.5 mL) was treated with triethylsilane (0.62 mL, 3.90 mmol). Vigorous magnetic stirring was necessary to obtain a homogeneous mixture for 30 min at 0°C. Water was added to the residue and the mixture was extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate and evaporated in vacuo. The crude material was recrystallized by ethyl acetate/hexane to give **12** (0.32 g 88%): m.p. 180–182°C; ^{1}H NMR ($CDCl_3$) δ 6.63 (s, 2H, ArH), 3.78 (s, 6H, OCH_3), 3.13–3.10 (m, 1H), 2.95–2.92 (m, 1H), 2.77–2.64 (m, 1H) 1.82–1.70 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 181.90, 151.28, 151.16, 126.01, 125.05, 106.90, 106.85, 55.59, 55.57, 39.09, 25.68, 24.77, 22.79; MS (m/z) 236 (M^+).

1-(5,8-Dimethoxy-1,2,3,4-tetrahydro-2-naphthalenyl)-1-ethanone (13). A stirred solution of carboxylic acid **12** (0.26 g, 1.10 mmol) in THF (10 mL) was cooled to 0°C on ice-bath and treated rapidly with 1.4 M methyl lithium in ether (3.1 mL, 4.4 mmol). After 2 hr at 0°C, chlrorotrimethyl silane (3 mL) was rapidly added while stirring continued. The ice bath was then removed and the reaction mixture allowed to room temperature at which

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point 30 mL of 1 N HCl was added, and the resulting two-phase system was stirred at room temperature for 0.5 hr. The mixture was then transferred into a separator funnel and extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate, filtered and removal of solvent from the filtrate in vacuo to give methyl ketone **13** (0.21 g, 81%): m.p. 83–85°C (lit.[12] 82–83°C); ^{1}H NMR ($CDCl_3$) δ 6.62 (s, 2H, ArH), 3.77 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.05–2.90 (m, 2H), 2.68–2.48 (m, 3H), 2.25 (s, 3H, $COCH_3$), 2.18–2.13 (m, 1H), 1.67–1.57 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 211.44, 151.22, 151.12, 126.14, 125.33, 106.81, 106.77, 55.48, 47.17, 28.04, 25.31, 24.31, 23.07; MS (m/z) 234 (M^+), 219 ($M^+ - CH_3$).

(±)-2-Acetyl-2-hydroxy-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalene (14). The mixture of 1 M *t*-BuOK (4.3 mL, 4.3 mmol), triethyl phosphite (0.38 mL, 2.2 mmol) in DMF (20 mL) was stirred at −15°C. Oxygen was bubbled through the solution (approximately 3 bubbles sec^{-1} from a disposable pipette). Then ketone **13** (0.23 g, 1.0 mmol) was added in a minimum amount of tetrahydrofuran. While the temperature was carefully maintained between −15°C and −10°C, the color of the reaction mixture changed from yellow to orange to red to dark red. By taking small aliquots and quenching these in water, one can monitor the reaction by TLC. After 1 hr, the reaction was quenched by addition of water (20 mL). The crude reaction mixture was stirred for 3 hr at ambient temperature, the DMF was removed under vacuum, and the resulting slurry was dissolved in dichloromethane. The organic phase was then washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated, and the triethyl phosphate was removed at 50°C (10^{-4} torr). The resulting oil was chromatographed on silica gel (ethyl acetate/hexane 1 : 3) to afford C_9-monohydroxylated β-tetralol (±)-**14** (0.21 g, 85%) as a white crystal: m.p. 100–102°C (lit.[4c,7b] 100–101°C); ^{1}H NMR ($CDCl_3$) δ 6.67 (d, 1H, $J = 8.8$ Hz, ArH), 6.64 (d, 1H, $J = 8.8$ Hz, ArH), 3.79 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.62 (s, 1H, OH), 2.75–2.99 (m, 4H), 2.32 (s, 3H, CH_3), 1.83–2.05 (m, 2H, CH); MS (m/z) 250 (M^+), 232 ($M^+ - H_2O$).

9-Acetyl-6,11-dihydroxy-7,8,9,10-tetrahydronaphthacen-5,12-dione (15). To a solution of **13** (0.75 g, 3.20 mmol) in nitrobenzene (30 mL) was added a solution of aluminum chloride (0.85 g, 6.40 mmol) in nitrobenzene (30 mL) at 0°C and the mixture was slowly warmed to room temperature for 30 min. Phthaloyl dichloride (0.51 mL, 3.52 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 (40 mL) and dichloromethane (50 mL) were added to the resulting solution and filtered. The water layer was extracted with dichloromethane and the combined organic layer was washed with saturated sodium bicarbonate and brine. After drying over anhydrous magnesium sulfate, the solvent was removed in vacuo and the crude material was purified by recrystalization (dichloromethane/diethyl ether/hexane) to afford **15** (0.94 g, 87%):

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

m.p. 198–201°C (lit.[15a] 199–201°C); ^{1}H NMR ($CDCl_3$) δ 13.52 (s, 1H, OH), 13.49 (s, 1H, OH), 8.30 (m, 2H, ArH), 7.80 (m, 2H, ArH), 3.10 (m, 2H, $C_{10}H$), 2.75 (m, 2H, C_7H), 2.31 (s, 3H, $COCH_3$), 1.95 (m, 1H, CH), 1.90 (m, 2H, CH_2); MS (m/z) 336 (M^+), 293 ($M^+ - COCH_3$).

(±)-9-Acetyl-6,9,11-trihydroxy-7,8,9,10-tetrahydronaphthacen-5,12-dione (16). Reaction of **14** (0.45 g, 1.80 mmol), phthaloyl dichloride (0.28 mL, 1.98 mmol) and aluminum chloride (0.49 g, 3.65 mmol) in nitrobenzene (40 mL) at 0°C was carried out as described for the preparation of **15** to yield **16** (0.54 g, 86%) as a red crystal: m.p. 216–218°C (lit.[4c] 214–216°C); ^{1}H NMR ($CDCl_3$) δ 13.48 (s, 2H, ArOH), 8.48–8.19 (m, 2H, ArH), 7.95–7.74 (m, 2H, ArH), 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 ($M^+ - COCH_3$).

(±)-9-Acetyl-6,7,9,11-tetrahydroxy-7,8,9,10-tetrahydronaphthacen-5,12-dione [(±)-3b]. A mixture ketone **16** (0.53 g, 1.50 mmol), ethylene glycol (0.84 g, 15.0 mmol), *p*-TsOH (0.04 g), in benzene (150 mL) was refluxed for 3–5 hr with azeotropic removal of water formed using a Dean–Stark apparatus. After cooling down, the mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate and the organic layer was separated. The aqueous layer was extracted with dichloromethane and the combined organic layer was washed with brine, dried with magnesium sulfate, concentrated in vacuo. The residue was recrystallized with dichlormethane/diethyl ether/hexane to afford the pure acetal (0.57 g, 95%) as a red powder.

A mixture of acetal (0.15 g, 0.38 mmol), *N*-bromosuccinimide (72.0 mg, 0.40 mmol), and catalytic amounts of AIBN (0.03 g, 0.18 mmol) in carbon tetrachloride was heated at reflux for 30 min with stirring under irradiation with a 500 W halogen lamp. After being cooled, silica gel (5 g, for column chromatography) and ice-cooled wet tetrahydrofuran (30 mL, containing about 3% water) were successively added to the mixture and stirred at r.t. for 1.5 hr. Silica gel was separated by filter 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 1 N hydrochloric acid (10 mL) and dioxane (20 mL), the acidic solution was stirred at 80°C for 1 hr 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 waster, then dried on anhydrous magnesium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (acetone/methanol/dichloromethane 2 : 1 : 20) to give enantiomeric mixture (±)-Idarubicinone (**3b**) (0.11 g, 78% overall yield). The enantiomeric ratio (1 : 1) was determined by HPLC analysis with a chiral column (Daicel Chiralcel OD-H; eluent, 20% isopropyl alcohol in hexane; flow rate, 0.5 mL min^{-1}; $R_t = 85$ min and 105 min): m.p. 175–177°C

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

(lit.[15a] 173–175, lit.[17a] 176–178°C); ^{1}H NMR (DMSO-d_6) δ 13.25 (s, 1H, OH), 13.10 (s, 1H, OH), 8.13–8.09 (m, 2H, ArH), 7.90–7.88 (m, 2H, ArH), 6.06 (s, 1H, $C_{7eq}H$), 5.26 (s, 1H, C_7OH), 4.91 (s, 1H, C_9OH), 2.93 (d, 1H, $J = 18.6$ Hz, $C_{10}H$), 2.77 (d, 1H, $J = 18.0$ Hz, $C_{10}H$), 2.31 (s, 3H, $COCH_3$), 2.16 (d, 1H, $J = 13.7$ Hz, C_8H), 1.90 (dd, 1H, $J = 14.2$, 4.39 Hz, C_8H); ^{13}C NMR (DMSO-d_6) δ 211.85, 186.06, 185.83, 156.16, 155.38, 136.85, 135.15, 134.96, 134.86, 132.70, 132.52, 126.47, 126.44, 110.36, 109.82, 76.24, 60.43, 35.71, 32.11, 24.45; MS (FAB$^+$, Na) m/z 391.0 $(M + Na)^+$.

3-Acetyl-3,5,12-trihydroxy-6,11-dioxo-1,2,3,4,6,11-hexahydro-1-naphthacenyl (2*R*)-2-(acetyloxy)-2-phenylethanoate (17). (±)-Idarubicinone **3b** (0.15 g, 0.41 mmol) and (*S*)-(+)-*O*-acetylmandelic acid (0.30 g, 1.54 mmol) in the presence of dicyclohexylcarbodiimide (DCC, 0.30 g, 1.45 mmol) and 4-(dimethylamino) pyridine (DMAP) (0.03 g, 0.24 mmol) in anhydrous dichloromethane were stirred at r.t. for 15 hr. After filtration of the precipitated urea, solvent was removed under reduced pressure and the residue was purified by column chromatography with acetone/dichloromethane (1 : 20) as eluent. Two products are obtained **17a** (0.11 g, 47%) and **17b** (0.09 g, 40%) as red crystals: **17a**; m.p. 98–100°C; $[\alpha]_D^{20}$ +77.7° (c 0.1, dichloromethane); IR (KBr) 2942, 2840, 1745, 1631, 1591, 1427, 1381, 1176, 1046, 983, 792, 741, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 13.31 (s, 1H, ArOH), 12.99 (s, 1H, ArOH), 8.35–8.31 (m, 2H, ArH), 7.83–7.86 (m, 2H, ArH), 7.48–7.51 (m, 2H, ArH), 7.39–7.36 (m, 3H, ArH), 6.36 (d, 1H, $J = 3.9$ Hz, OCOCH), 5.72 (s, 1H, $C_{7eq}H$), 3.32 (dd, 1H, $J = 2.0$, 18.6 Hz, $C_{10}H$), 2.95 (d, 1H, $J = 19.0$ Hz, $C_{10}H$), 2.46 (s, 3H, OCH_3), 2.27 (d, 1H, $J = 5.9$ Hz, C_8H), 2.24 (s, 3H, OCH_3), 2.2–2.17 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 212.29, 187.04, 186.40, 171.56, 168.09, 156.37, 155.98, 137.23, 134.61, 134.48, 133.47, 133.33, 132.36, 130.39, 129.39, 128.67, 127.34, 127.11, 126.97, 111.97, 110.62, 75.75, 75.59, 64.29, 33.74, 32.19, 30.92, 24.76, 20.73; UV λ_{max} (log ε) 252 (0.94), 258 (0.90), 283 (0.27), 487 (0.23). **17b**; m.p. 82–84°C; $[\alpha]_D^{20}$ +40.1° (c 0.1, CH_2Cl_2); IR (KBr) 2933, 1748, 1630, 1594, 1428, 1374, 1238, 1053, 982, 926, 789, 738, 685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 13.28 (s, 1H, ArOH), 13.27 (s, 1H, ArOH), 8.35–8.33 (m, 2H, ArH), 7.87–7.82 (m, 2H, ArH), 7.50–7.47 (m, 2H, ArH), 7.44–7.37 (m, 3H, ArH), 6.51 (d, 1H, $J = 4.4$ Hz, OCOCH), 5.96 (s, 1H, $C_{7eq}H$), 3.20 (dd, 1H, $J = 2.0$, 18.8 Hz, $C_{10}H$), 2.85 (d, 1H, $J = 19.0$ Hz, $C_{10}H$), 2.61 (s, 1H, C_9OH), 2.27 (s, 3H, OCH_3), 2.24–2.22 (m, 2H, CH_2), 2.20 (s, 3H, $COCH_3$), 2.18–2.17 (m, 2H, CH_2), 2.06–2.02 (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$) δ 211.43, 187.07. 186.46, 170.98, 167.22, 156.38, 155.82, 136.90, 134.68, 134.50, 133.47, 133.44, 133.26, 130.33, 129.59, 128.98, 127.89, 127.08, 127.06, 112.03, 110.74, 75.37, 74.83, 63.63, 34.38, 32.25, 30.92, 24.46, 20.80; UV λ_{max} (log ε) 253 (1.09), 258 (1.09), 487 (0.26).

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

(7*S*,9*S*)-9-Acetyl-6,7,9,11-tetrahydroxy-5,7,8,9,10,12-hexahydro-5,12-naphthacenedione, (7*S*,9*S*)-(+)-idarubicinone [(+)-3b]. A solution of **17a** (0.55 g, 1.01 mmol) in dichloromethane (50 mL) and saturated aqueous NaOH solution (5 drops) was stirred at room temperature. After 2 hr, 1 N HCl (50 mL) was added and the resulting mixture was stirred for 0.5 hr. The mixture was then transferred into a separator funnel and extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate and removal of solvent from the residue in vacuo gave enantiomerically pure idarubicinone (+)-**3b** (0.32 g, 86%) as reddish brown crystals: m.p. 184–185°C; $[\alpha]_D^{20}$ +159° (c 0.1, dioxane), (lit.[17b] m.p. 184–185°C; $[\alpha]_D^{20}$ +154°, c 0.1, dioxane, lit.[4c] m.p. 183.5–184.5°C, $[\alpha]_D^{20}$ +153°, c 0.09, dioxane); IR (KBr) 3442, 2943, 1710, 1629, 1594, 1425, 1384, 1238, 1133, 985, 921, 784, 734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.24 (s, 1H, OH), 12.96 (s, 1H, OH), 8.12–8.25 (m, 2H, ArH), 7.68–7.85 (m, 2H, ArH), 5.22 (m, 1H, C_7H, $\nu_{1/2} = 12.0$ Hz), 4.61 (s, 1H, C_9OH), 3.90 (d, 1H, $J = 6.0$ Hz, C_7OH), 3.12 (dd, 1H, $J = 18.0$, 1.0 Hz, $C_{10}H_{eq}$), 2.88 (d, 1H, $J = 18.0$ Hz, $C_{10}H_{ax}$), 2.44 (s, 3H, $COCH_3$), 2.32 (br d, 1H, $J = 16.0$ Hz, C_8H_{eq}), 2.12 (dd, 1H, $J = 16.0$, 4.0 Hz, C_8H_{ax}); ^{13}C NMR (DMSO-d_6) δ 211.85, 186.06, 185.83, 156.16, 155.38, 136.85, 135.15, 134.96, 134.86, 132.70, 132.52, 126.47, 126.44, 110.36, 109.82, 76.24, 60.43, 35.71, 32.11, 24.45; UV λ_{max} (log ε) 252 (1.50), 485 (0.38), 288 (0.40); MS (FAB^+, Na) m/z 391.0 $(M + Na)^+$.

(7*R*,9*R*)-9-Acetyl-6,7,9,11-tetrahydroxy-5,7,8,9,10,12-hexahydro-5,12-naphthacenedione, (7*R*,9*R*)-(−)-idarubicinone [(−)-3b]. Reaction of **17b** (0.51 g, 0.94 mmol), and saturated aqueous NaOH in dichloromethane was carried out as described for the preparation of (+)-**3b** to yield enantiomerically pure (−)-idarubicinone (−)-**3b** (0.29 g, 85%) as reddish brown crystals: m.p. 183.5–184.5°C; $[\alpha]_D^{20}$ −156° (c 0.1, dioxane); IR (KBr) 3432, 2952, 2584, 1714, 1614, 1590, 1443, 1375, 1240, 1129, 1036, 990, 790, 738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.24 (s, 1H, OH), 12.96 (s, 1H, OH), 8.12–8.25 (m, 2H, ArH), 7.68–7.85 (m, 2H, ArH), 5.22 (m, 1H, C_7H, $\nu_{1/2} = 12.0$ Hz), 4.61 (s, 1H, C_9OH), 3.90 (d, 1H, $J = 6.0$ Hz, C_7OH), 3.12 (dd, 1H, $J = 18.0$, 1.0 Hz, $C_{10}H_{eq}$), 2.88 (d, 1H, $J = 18.0$ Hz, $C_{10}H_{ax}$), 2.44 (s, 3H, $COCH_3$), 2.32 (br d, 1H, $J = 16.0$ Hz, C_8H_{eq}), 2.12 (dd, 1H, $J = 16.0$, 4.0 Hz, C_8H_{ax}); ^{13}C NMR (DMSO-d_6) δ 211.85, 186.06, 185.83, 156.16, 155.38, 136.85, 135.15, 134.96, 134.86, 132.70, 132.52, 126.47, 126.44, 110.36, 109.82, 76.24, 60.43, 35.71, 32.11, 24.45; UV λ_{max} 252 (1.42), 485 (0.36), 288 (0.34); Mass (FAB^+, Na) m/z 391.0 $(M + Na)^+$.

Methyl-3,4,5-tri(acetyloxy)-6-{[(1*S*,3*S*)-3-acetyl-3,5,12-trihydroxy-6,11-dioxo-1,2,3,4,6,11-hexahydro-1-naphthacenyl]oxy}tetrahydro-2H-2-pyrancarboxylate, (7*S*,9*S*)-(+)-idarubicinone-7-methyl(tri-*O*-acetyl-ester)-β-D-glucuronide (18). A suspension of (+)-idarubicinone (+)-**3b** (0.20 g, 0.54 mmol), acetobromo-α-D-glucuronic acid methyl ester (0.32 g,

0.81 mmol) and 4 Å molecular sieves (0.60 g) in dry dichloromethane (50 mL) was stirred for 30 min at room temperature. Then, anhydrous $ZnBr_2$ (0.31 g, 1.35 mmol) was added and the resulting suspension was refluxed for 48 hr with stirring. More dichloromethane (50 mL) was added, the suspension was filtered through celite and stirred for 20 min with a saturated aqueous solution of $NaHCO_3$ (50 mL). The aqueous phase was separated, washed with dichloromethane, the organics were combined, washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was passed through a silica gel column (dichloromethane/MeOH/acetone = 20 : 1 : 2 → dichloromethane/acetone = 15 : 1) to give stereochemically pure β-anomer **18** (0.21 g, 56%) as a orange powder: m.p. 274–278°C; $[\alpha]_D^{20}$ +45.5° (c 1.0, dichloromethane); IR (KBr) 3839, 3742, 3618, 3100, 1751, 1723, 1626, 1540, 1418, 1405, 1230, 1063, 1043, 794, 668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.67 (s, 1H, ArOH), 13.28 (s, 1H, ArOH), 8.36–8.34 (m, 2H, ArH), 7.86–7.27 (m, 2H, ArH), 5.38 (t, 1H, $J = 9.3$ Hz, $C_{3'}H$), 5.35 (s, 1H, $C_{7eq}H$), 5.25 (t, 1H, $J = 9.8$ Hz, $C_{4'}H$), 5.16 (d, 1H, $J = 7.8$ Hz, $C_{1'}H$), 4.98 (t, 1H, $J = 8.3$, 8.8 Hz, $C_{2'}H$), 4.18 (d, 1H, $J = 9.8$ Hz, $C_{5'}H$), 4.17 (s, 1H, C_9–OH), 3.80 (s, 3H, $COOCH_3$), 3.24 (d, 1H, $J = 19.5$ Hz, $C_{10eq}H$), 3.00 (d, 1H, $J = 19.0$ Hz, $C_{10ax}H$), 2.63 (d, 1H, $J = 15.1$ Hz, $C_{8eq}H$), 2.46 (s, 3H, $COCH_3$), 2.08 (dd, 1H, $C_{8ax}H$), 2.05 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.85 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$) δ 213.29, 186.86, 186.79, 170.01, 169.46, 169.36, 167.05, 156.41, 156.40, 137.43, 134.66, 134.62, 133.40, 133.38, 132.06, 127.19, 127.05, 111.66, 110.59, 101.48, 76.24, 72.36, 71.54, 71.06, 70.27, 69.37, 53.03, 35.07, 33.49, 25.14, 20.61, 20.52, 20.48; UV λ_{max} (log ε) 253(0.86), 258 (0.83); MS (FAB^+, Na) m/z 706.8 $(M + Na)^+$.

Methyl-3,4,5-tri(acetyloxy)-6-{[(1*R*,3*R*)-3-acetyl-3,5,12-trihydroxy-6,11-dioxo-1,2,3,4,6,11-hexahydro-1-naphthacenyl]oxy}tetrahydro-2H-2-pyrancarboxylate, (7*R*,9*R*)-(−)-idarubicinone-7-methyl (tri-*O*-acetyl-ester)-β-D-glucuronide (19). Reaction of (−)-idarubicinone (−)-**3b**, (0.27 g, 0.73 mmol), acetobromo-α-D-glucuronic acid methyl ester (0.44 g, 1.10 mmol), 4 Å molecular sieves (0.60 g) and $ZnBr_2$ (0.41 g, 1.83 mmol) in dichloromethane was carried out as described for the preparation of **18** to yield stereochemically pure β-anomer **19** (0.26 g, 53%) as a orange powder: m.p. 214–218°C; $[\alpha]_D^{20}$ −79.8° (c 0.01, dichloromethane); IR (KBr) 3838, 3739, 3674, 3651, 3526, 2955, 1757, 1718, 1624, 1588, 1417, 1375, 1230, 1041, 985, 791, 735, 672 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.71 (s, 1H, ArOH), 13.27 (s, 1H, ArOH), 8.35–8.32 (m, 2H, ArH), 7.85–7.27 (s, 2H, ArH), 5.51 (s, 1H, $C_{7eq}H$), 5.32 (t, 1H, $J = 9.3$ Hz, $C_{3'}H$), 5.15 (t, 1H, $J = 9.8$ Hz, $C_{4'}H$), 5.05 (d, 1H, $J = 8.3$ Hz, $C_{1'}H$), 4.96 (t, 1H, $J = 9.3$, 8.3 Hz, $C_{2'}H$), 4.16 (s, 1H, C_9–OH), 4.03 (d, 1H, $J = 9.8$ Hz, $C_{5'}H$), 3.47 (s, 3H, $COOCH_3$), 3.26 (d, 1H, $J = 19.5$ Hz, $C_{10eq}H$), 3.06 (d, 1H, $J = 19.5$ Hz, $C_{10ax}H$), 2.42 (s, 3H, OAc), 2.30 (d, 1H, $J = 14.6$ Hz, $C_{8eq}H$), 2.13 (dd, 1H, $C_{8ax}H$), 2.11 (s, 3H, OAc),

MARCEL DEKKER, INC.
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2.02 (s, 3H, OAc), 2.00 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$) δ 212.12, 186.80, 186.50, 170.08, 169.55, 169.30, 166.56, 156.60, 156.04, 136.95, 134.60, 134.53, 133.42, 133.32, 132.47, 127.18, 126.78, 111.72, 110.59, 100.95, 75.93, 72.43, 71.94, 71.12, 70.05, 69.22, 52.67, 34.27, 34.23, 24.84, 20.73, 20.59, 20.48; UV λ_{max} ($\log \varepsilon$) 252 (0.74), 258 (0.71); MS (FAB$^+$, Na) m/z 706.8 $(M + Na)^+$.

6-{[1*S*,3*S*]-3-Acetyl-3,5,12-trihydroxy-6,11-dioxo-1,2,3,4,6,11-hexahydro-1-naphthacetyl}oxy}-3,4,5-trihydoxytetrahydo-2H-2-pyrancarboxylic acid, (7*S*,9*S*)-(+)-idarubicinone-7-β-D-glucuronide (20). To a solution of **18** (30.0 mg, 0.044 mmol) in MeOH/THF (5 : 1, v/v) was added 2.6 mL (6.0 eq) of a 0.1 N LiOH solution, the resulting deep blue solution was stirred at 0°C under an argon atmosphere. Progress of the deprotection was monitored on reversed-phase TLC (SiO_2-C_{18} MeCN/H_2O, 1/2). After 2 hr of deprotection, the reaction mixture was diluted with 10 mL of water and neutralized by adding ca. 200 mg of amberlite cation exchange resin (H^+ form), 2 mL of THF was added to homogenize the suspension. The amberlite resin was removed by filtration. The MeOH and THF suspended in the water layer were removed by evaporation and the red aqueous product solution was transferred to a reversed phase column packed with RP-C18 material. The column was successively washed with MeCN/H_2O (1 : 3, v/v) to elute the product and the MeCN was removed by evaporation and removal of water from the residue in vacuo to give 20.0 mg (84%) of compound **20** as a reddish orange powder: m.p. 130°C (decomp); $[\alpha]_D^{20}$ +60.0° (c 0.1, MeOH/H_2O); IR(KBr) 3482.38, 2949.93, 2889.94, 1699.07, 1620.56, 1586.92, 1418.69, 1347.66, 1250.47, 1198.13, 1063.55, 861.25, 835.00, 735.63, 690.63, 658.75 cm^{-1}; ^{1}H NMR (CD_3OD) δ 8.27 (m, 2H, ArH), 7.87 (m, 2H, ArH), 5.21 (d, 1H, J = 2.93 Hz, $C_{1'}$H), 4.82 (s, 1H, C_{7eq}H), 4.80 (s, 1H, OH), 3.71 (d, 1H, J = 9.3 Hz, $C_{5'}$H), 3.50–3.42 (m, 2H, $C_{3'}$H, $C_{2'}$H), 3,33 (s, 1H, OH), 3.23 (t, 1H, J = 8.3, 8.8 Hz, $C_{4'}$H), 3.08 (d, 1H, J = 2.5 Hz, C_{10eq}H), 2.78 (m, 2H, C_{8eq}, C_{10ax}), 2.41 (s, 3H, CH_3), 2.10 (dd, 1H, J = 15.1, 4.88 Hz, C_{8ax}H); ^{13}C NMR (CD_3OD) δ 215.45, 188.23, 187.84, 176.85, 157.87, 157.01, 137.60, 135.77, 135.08, 134.79, 134.60, 127.90, 112.53, 111.82, 106.00, 77.48, 77.35, 76.58, 75.15, 73.75, 71.71, 36.29, 33.33, 25.13; UV λ_{max} ($\log \varepsilon$) 251 (2.85), 287 (1.35), 484 (1.42); MS (FAB$^+$, Na) m/z 567.2 $(M + Na)^+$.

6-{[1*R*,3*R*]-3-Acetyl-3,5,12-trihydroxy-6,11-dioxo-1,2,3,4,6,11-hexahydro-1-naphthacetyl}oxy}-3,4,5-trihydoxytetrahydo-2H-2-pyrancarboxylic acid, (7*R*,9*R*)-(−)-idarubicinone-7-β-D-glucuronide (21). To a solution of **19** (20.0 mg, 0.029 mmol) in MeOH/THF (5 : 1, v/v) was added 1.8 mL (6.0 eq) of a 0.1 N LiOH solution and the resulting deep blue solution was stirred at 0°C under an argon atmosphere. Progress of the deprotection was monitored on reversed-phase TLC (SiO_2-C_{18} MeCN/H_2O, 1/2). After 2 hr

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of deprotection, the reaction mixture was diluted with 8 mL of water and neutralized by adding ca. 150 mg of amberlite cation exchange material (H^+ form), 2 mL of THF was added to homogenize the suspension. The amberlite resin was removed by filtration. The MeOH and THF suspended in the water layer were removed by evaporation and the red aqueous product solution was transferred to a reversed phase column packed with RP-C18 material. The column was successively washed with $MeCN/H_2O$ (1/3, v/v) to elute the product and the MeCN was removed by evaporation and removal of water from the residue in vacuo to give 13.0 mg (82%) of compound **21** as a reddish orange powder: m.p. 224°C (decomp); $[\alpha]_D^{20}$ −74.0° (c 0.1, $MeOH/H_2O$); IR (KBr) 3482.38, 2957.43, 2837.44, 1703.43, 1646.73, 1459.81, 1414.95, 1201.87, 1056.07, 1029.91, 1018.69, 833.13, 752.50, 641.88 cm^{-1}; ^1H NMR (CD_3OD) δ 8.35 (m, 2H, ArH), 7.89 (m, 2H, ArH), 5.35 (m, 1H, $C_{1'}H$), 4.93 (s, 1H, $C_{7eq}H$), 3.54–3.45 (m, 3H, $C_{5'}H$, $C_{3'}H$, $C_{2'}H$), 3.11 (m, 2H, $C_{4'}H$, $C_{10eq.}$), 2.78 (m, 1H, C_{10ax}), 2.60 (d, 1H, $J = 16.6$ Hz, C_{8eq}), 2.36 (s, 3H, CH_3), 2.14 (m, 1H, $C_{8ax}H$); UV λ_{max} ($\log \varepsilon$) 251 (2.75), 286 (1.29), 485 (1.45); MS (FAB^+, Na) m/z 567.2 $(M + Na)^+$.

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REFERENCES

1. (a) Priebe, W. *Anthracycline Antibiotics, New analogues, Methods of Delivery, and Mechanisms of Actions*; ACS Symposium Series 574, American Chemical Society: Washington, DC, 1995, 100–114; (b) Arcamone, F. Doxorubicin. In *Anticancer Antibiotics*; Medicinal Chemistry, A Series of Monographs volume 17; Academic Press: London, 1981; Vol. 17, 1–369; (c) Mettler, F.P.; Young, D.M.; Ward, J.M. Adriamycin-induced cardiotoxicity (cardiomyopathy and congestive heart failure) in rats. Cancer Res. **1977**, *37*, 2705.
2. (a) Arcamone, F.; Bernardi, L.; Giardino, B.; Patelli, B.; DiMarco, A.; Pratesi, G.; Reggiani, P. Synthesis and antitumor activity of 4-demethoxydaunorubicin, 4-demthoxy-7,9-diepidaunorubicin, and their β anomers. Cancer Treatment Rep. **1976**, *60*, 829–834; (b) Casazza, A.M. Exper-

imental evaluation of anthracycline analogs. Cancer Treatment Rep. **1979**, *63*, 835–844.
3. Hollingshead, L.M.; Faulds, D. Idarubicin. Drugs **1991**, *42*, 690–719.
4. (a) Badalassi, F.; Crotti, P.; Di Bugno, C.; D'Arata, F.; Favero, L.; Ramacciotti, A. Efficient enantioselective synthesis of (*R*)-2-acetyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene, the key intermediate in the synthesis of anthracycline antibiotics. Tetrahedron: Asymmetry **2001**, *12*, 3155–3161; (b) Sekine, A.; Ohshima, T.; Shibasaki, M. An enantioselective formal synthesis of 4-demethoxydaunomycin using the catalytic asymmetric ring opening reaction of *meso*-epoxide with *p*-anisidine. Tetrahedron **2002**, *58*, 75–82; (c) Tanno, N.; Terashima, S. Development of a novel synthetic route to optically active anthracyclinones: preliminary synthesis of the racemic key intermediate. Chem. Pharm. Bull. **1983**, *31*, 811–820; (d) Krohn, K. Synthesis of anthracyclinones by electrophilic and nucleophilic addition to anthraquinones. Tetrahedron **1990**, *46*, 291–318; (e) Penco, S.; Angelucci, F.; Vigevani, A.; Arlandin, E.; Arcamone, F. Stereochemical requirements in the antitumour anthracyclines. J. Antibiot. **1977**, *30*, 764–766.
5. (a) Rukhman, I.; Gutman, A.L. Synthesis of morphine 6-α-D-glucuronide. Tetrahedron Lett. **2000**, *41*, 6889–6892; (b) Ramu, K.; Baker, J.K. Synthesis, characterization, and antimalarial activity of the glucuronides of the hydroxylated metabolites of arteether. J. Med. Chem. **1995**, *38*, 1911–1921; (c) Mitchell, M.B.; Whitcombe, I.W.A. The synthesis of the glucuronide adduct of trocade. Tetrahedron Lett. **2000**, *41*, 8829–8834.
6. (a) Leenders, R.G.G.; Damen, E.W.P.; Bijsterveld, E.J.A.; Scheeren, H.W.; Houba, P.H.J.; Meulen-Muileman, I.H.; Boven, E.; Haisma, H. Novel anthracycline-spacer-β-glucuronide, -β-glucoside, and -β-galactoside prodrugs for application in selective chemotherapy. J. Bioorg. Med. Chem. **1999**, *7*, 1597–1610; (b) Takagi, Y.; Kobayashi, N.; Chang, M.S.; Lim, G.J.; Tsuchiya, T. Synthesis and antitumor activity of the 7-*O*-(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)daunomycinone derivatives modified at C-3′ or C-4′. Carbohyd. Res. **1998**, *307*, 217–232; (c) Zunino, F.; Pratesi, G.; Perego, P. Role of the sugar moiety in the pharmacological activity of anthracyclines: development of a novel series of disaccharide analogs. Biochem. Pharmaco. **2001**, *61*, 933–938.
7. (a) Rho, Y.S.; Park, S.; Kim, W.-J.; Kim, G.; Yoo, D.J.; Kang, H.S.; Chung, S.-R. Synthesis of new anthracycline derivatives containing pyruvic, aspartic or *N*-acetylaspartic acid molecule. J. Synth. Commun. **2002**, *32* (13), 1961–1975; (b) Rho, Y.S.; Park, S.H.; Cho, I.H.; Lee, C.H.; Kang, H.S.; Cheong, C.J. Syntheses of novel 9-fluoroantracylcine deriva-

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tives. Bull. Kor. Chem. Soc. **1998**, *19*, 74–78; (c) Rho, Y.S.; Ko, H.K.; Sin, H.S.; Yoo, D.J. A facile total synthesis of idarubicinone. Bull. Kor. Chem. Soc. **1999**, *20*, 1517–1520; (d) Rho, Y.S.; Ko, H.K.; Kim, W.-J.; Yoo, D.J.; Kang, H.S. Total synthesis of a new 7-deoxyidarubicinone derivative through the functionalization of an Λ-ring side chain. Bull. Kor. Chem. Soc. **2000**, *21*, 774–778.

8. Ramana, M.P.V.; Potnis, P.V. Tandem acylation-cycloalkylation with cyclohexane l-acetic acid: a new entry to aporphine alkaloids. Tetrahedron Lett. **1996**, *37*, 1671–1674.
9. Bastian, J.A.; Lash, T.D. Porphyrins with oxocylcic rings. Part 12. Synthesis of *meso*, *β*-butano- and *meso*, *β*-pentanoporphyrins from cycloalka[*b*]pyrroles. Tetrahedron **1998**, *54*, 6299–6310.
10. Kudav, N.A.; Kulkarni, M.D.; Kochrekar, D.A. A new and simple approach for the synthesis of 3-acetyl-3,4-dihydro-1(2H)-naphthalenones and 3,4-dihydro-3-(2-methyl-1,3-dithiolan-2-yl)-l(2II)-naphthalenones. J. Indian Chem. Soc. **2002**, *79*, 62–64.
11. Chenard, B.L.; Dolson, M.G.; Sercel, A.D.; Swenton, J.S. Annelation reactions of quinone monoketals. Studies directed at an efficient synthesis of anthracyclinones. J. Org. Chem. **1984**, *49*, 318–325.
12. Lown, J.W.; Sondhi, S.M.; Mandal, S.B.; Murphy, J. Synthesis and redox properties of chromophore modified glycosides related to anthracyclines. J. Org. Chem. **1982**, *47*, 4304.
13. (a) Tanaka, H.; Yoshioka, T.; Shimauchi, Y.; Yoshimoto, A.; Ishikura, T. Synthetic approaches to new anthracyclines: 4,11-didoexy-2-hydroxy-*β*-rhodomycinone and its glycosides. Tetrahedron Lett. **1984**, *25*, 3355–3358; (b) Coburn, C.E.; Anderson, K.; Swenton, J.S. Convenient AB-ring segments for anthracyclinone synthesis via bishhydroxylation of 2-ethyl-5,8-dimethoxy-7-bromo-1-tetralone. J. Org. Chem. **1983**, *43*, 1455–1461.
14. (a) Sartori, G.; Casnati, G.; Bigi, F.; Robles, P. Metal template ortho-acylation of phenols: a new general approach to anthracyclinones. Tetrahedron Lett. **1987**, *28*, 1533–1536; (b) Nakajima, M.; Tomioka, K.; Koga, K. Short-step asymmetric syntheses of anthracycline antibiotics via enantioselective dihydroxylation by osmium tetroxide with a chiral diamine. Tetrahedron **1993**, *49*, 10807–10816.
15. (a) Doninguez, D.; Ardecky, R.J.; Cava, M.P. An improved route to 4-demethoxydaunomycinone. A-Ring functionalization and resolution studies of tetracyclic precursors. J. Am. Chem. Soc. **1983**, *105*, 1608–1613; (b) Ayyangar, N.R.; Mehendale, A.R.; Argade, A.B. 4-Bromo-2-acetoketal-1-butyraldehyde. An elegant key intermediate for the synthesis of 4-demethoxy-7,9-dideoxydaunomycinone by Marschalk reaction. Synth. Commun. **1987**, *17* (16), 1959–1964.

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16. Tamura, Y.; Akai, S.; Kishimoto, H.; Sasho, M.; Kirihara, M.; Kita, Y. Total synthesis 11-deoxyanthracyclines: 4-demethoxy-11-deoxydaunomycinone, 11-deoxydaunomycin, and their analogues. Chem. Pharm. Bull. **1988**, *36*, 3897–3914.
17. (a) Allen, J.G.; Hentemann, M.F.; Danishefsky, S.J. A powerful *o*-quinone dimethide strategy for intermolecular Diels-Alder cycloadditions. J. Am. Chem. Soc. **2000**, *122*, 571–575; (b) Kimura, Y.; Suzuki, M.; Matsumoto, T.; Abe, R.; Terashima, S. A simple and efficient synthesis of optically active (+)-4-demethoxydaunomycinone. Bull. Chem. Soc. Jpn. **1986**, *59*, 415–421.
18. Bollenback, G.N.; Long, J.W.; Benjamin, D.G.; Lindquist, J.A. The synthesis of aryl-D-glucopyranosiduronic acids. J. Am. Chem. Soc. **1955**, *77*, 3310–3315.
19. Koenigs, W.; Knorr, E. Über einige derivate des traubenzuckers und der glaktose. Ber. **1901**, *34*, 957–981.
20. Farrant, R.D.; Spraul, M.; Wilson, I.D.; Nicholls, A.W.; Nicholson, J.K.; Lindon, J.C. Assignment of the 750 MHz ^{1}H NMR resonances from a mixture of transacylated ester glucuronic acid conjugates with the aid of over sampling and digital filtering during acquisition. J. Pharm. Biomed. Anal. **1995**, *13*, 971–977.
21. (a) Luo, H.; Hawes, E.M.; McKay, G.; Midha, K.K. Synthesis and characterization of quaternary ammonium-linked glucuronide metabolites of drugs with an aliphatic tertiary amine group. J. Pharm. Sci. **1992**, *81*, 1079–1083; (b) Kaspersen, F.M.; Van Boeckel, C.A.A. A review of the methods of chemical synthesis of sulphate and glucuronide conjugates. Xenobiotica **1987**, *17*, 1451–1471.

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