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GOMEZ & DIAZ
ABOGADOS ASOCIADOS

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Doctora

ALIX CARMENZA CESPEDES DE VERGEL
JEFE DE LA DIVISION DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E.

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D.

REF: **EXPEDIENTE No. 03.040.538**
ASUNTO: PATENTE DE INVENCION – ENTRADA EN
FASE NACIONAL – CAPITULO II PRESENTADA EL 15
DE MAYO DE 2003
TITULO: PROCESO PARA LA SINTESIS DE
ANTRACICLINAS OPTICAMENTE ACTIVAS
CLASE: C07H 15/252
INVENTORES: CRISTINA DI BUGNO
FABIO D'ARATA
ALESSIO RAMACCIOTTI
PAOLO CROTTI
SOLICITANTE: MENARINI RICERCHE S.p.A.

DORA MARIA GOMEZ DIAZ, mayor de edad, vecina de esta ciudad de Bogotá Distrito Capital, República de Colombia, abogada en ejercicio e identificada como aparece al pie de mi firma, obrando en mi calidad de apoderada de la sociedad **MENARINI RICERCHE S.p.A.**, con domicilio en **Vía Tito Speri, 10, I-00040 Pomezia - ITALIA**, por medio del presente escrito y de conformidad con lo ordenado por su Despacho mediante **OFICIO No. 12583, REQUERIMIENTO** que fue **NOTIFICADO POR ESTADO EL 05 DE OCTUBRE DE 2007, estando dentro del término de tres (3) meses concedido por su Despacho**, me permito manifestar a su entidad que, los **DOCUMENTOS** que fueron solicitados por su Despacho en el oficio antedicho, **ya obran dentro del expediente**, los cuales se allegaron con la solicitud de **PATENTE DE INVENCION - ENTRADA EN FASE NACIONAL** el **15 DE MAYO DE 2003**, a saber:

I.- RAO, A. V. RAMA ET AL: "A Stereoconvergent Synthesis of (+)-4-Demethoxydaunomycin" J. CHEM. SOC., CHEM. COMMUN. (1984), (7), 453-5, XP002188353. Documento completo, particularmente página 454.

Este documento completo obra dentro del expediente bajo los FOLIOS 16, 16(ANVERSO) y 17. Aparecen las páginas 453, 454 y 455 del mencionado documento.

- 2 -

II.- RHO, YOUNG S. ET AL: "Total Synthesis of a New 7-Deoxydarubicinone Derivative through the Functionalization of and A-Ring Side Chain". BULL. KOREAN CHEM. SOC. (2000), 21(8), 774-778. XP001058968. Documento completo, particularmente páginas 774, 775, 778.

Este documento completo obra dentro del expediente bajo los FOLIOS 18, 18(ANVERSO), 19, 19(ANVERSO) y 20. Aparecen las páginas 774, 775, 776, 777 y 778 del mencionado documento.

III.- DATABASE CA. CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TANNO NORIHIKO ET AL: "Preparation of dihydroxytetrahydronaphthacenedione derivatives as intermediates for anthracycline antibiotics" recuperado de STN. Base de datos acceso No. 108:21533 XP002188593. Extracto, en particular CAS RN 11207-70-2&JP 62132838 A (SUMITOMO PHARMACEUTICALS CO., LTD., JAPAN) 16/06/87.

Este documento obra dentro del expediente bajo los FOLIOS 21, 21(ANVERSO) y 22.

IV.- NAKAJIMA, M. ET AL: "Short-Step Asymmetric Syntheses of Anthracycline Antibiotics via Enantioselective Dihydroxylation by Osmium Tetroxide with a Chiral Diamine". TETRAHEDRON Vol 49, No. 47, 1993, páginas 10807-10816, XP002188355. Citado en la solicitud el documento completo.

Este documento completo obra dentro del expediente bajo los FOLIOS 23, 23(ANVERSO), 24, 24(ANVERSO), 25, 25(ANVERSO), 26, 26(ANVERSO), 27 y 27(ANVERSO). Aparecen las páginas 10807, 10808, 10809, 10810, 10811, 10812, 10813, 10814, 10815 y 10816 del mencionado documento.

V.- RAO, A. V. RAMA ET AL: "Total Synthesis of (+)-4-Demethoxydaunomycinone" INDIAN J. CHEM., SECT. B (1985), 24B(7), 697-702 XP008000090. Documento completo, particularmente páginas 698, 700.

Este documento completo obra dentro del expediente bajo los FOLIOS 28, 28(ANVERSO), 29, 29(ANVERSO), 30 y 30(ANVERSO). Aparecen las páginas 697, 698, 699, 700 y 701 del mencionado documento.

Para el buen orden de sus registros, acompañamos nuevamente los DOCUMENTOS enunciados en los numerales I.-, II.-, III.-, IV.- y V.-, los cuales, reitero, ya obran dentro del expediente bajo los FOLIOS 16 al 30.

Consecuencialmente con lo anterior y toda vez que, la DOCUMENTACION solicitada por su Despacho mediante OFICIO No. 12583 ya obra en el expediente, la cual se está adjuntando nuevamente dentro del término concedido de tres (3) meses siguientes a la fecha de notificación del OFICIO No. 12583 proferido por esa Entidad, dando cabal cumplimiento a lo requerido en ese oficio, solicito a su Despacho se sirva continuar con el EXAMEN DE PATENTABILIDAD a la patente epigrafiada, la cual, como es de su conocimiento,

- 3 -

**ya fue PUBLICADA el 30 DE SEPTIEMBRE DE 2004 como consta en la GACETA
NUMERO 544 – PAGINA 348.**

NOTIFICACIONES

Le informo a usted que la sociedad poderdante y la suscrita recibiremos notificaciones en la Carrera
7 No. 32 - 85 oficina 501 de este Distrito Capital de Bogotá.

Atentamente,



DORA MARIA GOMEZ DIAZ

**C.C. No. 52'145.354 de Santafé de Bogotá
D.C.**

T.P. No. 95.718 del C.S. de la J.

**ANEXO: LO ANUNCIADO
DMGD/**

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XP-002188353

A Stereoconvergent Synthesis of (+)-4-Demethoxydaunomycin†

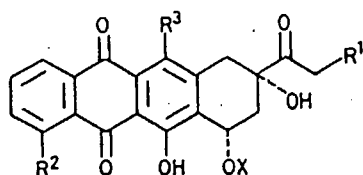
A. V. Rama Rao,* J. S. Yadav, K. Bal Reddy, and A. R. Mehendale
National Chemical Laboratory, Poona 411 008, India

Sharpless kinetic asymmetric epoxidation on $(\pm)$ -2-(1-hydroxyethyl)-5,8-dimethoxy-3,4-dihydronaphthalene [(8)] followed by LiAlH_4 reduction gave *R*-(-)-2-(*S*-1-hydroxyethyl)-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene [(-)-(10)] and the undesired antipode: the former was converted into *R*-(-)-2-acetyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene [*R*-(-)-(3)] while the latter was epimerized and recycled.

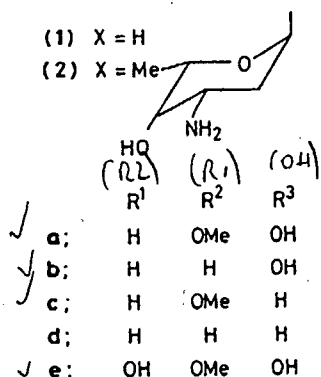
We have recently reported¹ a number of methods for the synthesis of racemic anthracyclones (1), the aglycones of antitumour anthracyclines (2), such as daunomycinone (1a),

4-demethoxydaunomycinone (1b), 11-deoxydaunomycinone (1c), and 4-demethoxy-11-deoxydaunomycinone (1d). However, studies on the structure-activity relationships have indicated that 4-demethoxydaunomycin (2b), not available by fermentation methods, is *ca.* 10 times more effective than natural daunomycin (2a) or adriamycin (2e) and clinical trials

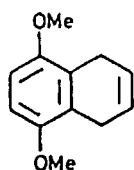
† This work forms part of the Ph.D. Dissertation of K. Bal Reddy, University of Poona, July 1983.



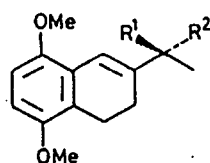
- (1) X = H
(2) X = Me



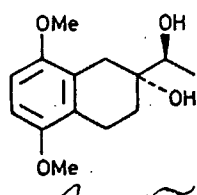
	(R ₁)	(R ₂)	(R ₃)
a:	H	OMe	OH
b:	H	H	OH
c:	H	OMe	H
d:	H	H	H
e:	OH	OMe	OH



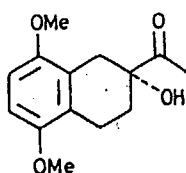
(5)



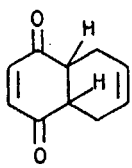
(8a) R¹ = OH, R² = H
(8b) R¹ = H, R² = OH



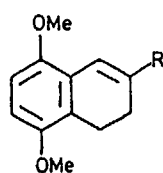
(1b)



(3)



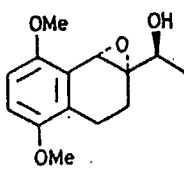
(4)



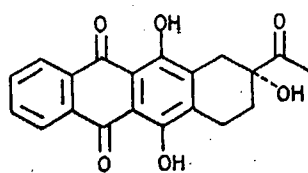
(6) R = H

(7) R = CHO

(8) R = CH(OH)Me



(9)



(-)-(11)

are reported to be promising.² Although numerous syntheses of anthracyclinones have been reported, the original assemblage of Wong *et al.*³ for the tetracyclic system of AB + CD coupling, making use of the key intermediate, 2-acetyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (3), has proved to be the most practical approach for the synthesis of natural and synthetic anthracyclinones including (1b). Consequently, numerous approaches have been developed for the synthesis of (3) and this compound has been resolved to obtain optically pure R-(-)-(3).⁴ We now wish to report a practical and convenient method of preparing R-(-)-(3) via Sharpless asymmetric epoxidation⁵ (kinetic resolution

method) of the racemic allylic alcohol (8) prepared from benzoquinone. The undesired antipode (8b) is then epimerized and recycled. Our present method is exceptionally simple and easy to operate for the synthesis of a variety of aglycones in optically active form.

Diels-Alder reaction of benzoquinone with butadiene in acetic acid at room temperature (r.t.) afforded the adduct (4) in 90% yield.⁶ O-Methylation (Me₂SO₄, K₂CO₃, boiling acetone, 4 h) gave 5,8-dimethoxy-1,4-dihydronaphthalene⁷ (5). Base catalysed isomerization of (5) (Bu^tOK, Me₂SO, r.t., N₂) resulted in the formation of 5,8-dimethoxy-3,4-dihydronaphthalene (6) in 100% yield.[†] [Colourless crystals, hexane, m.p. 70°C, ¹H n.m.r. (CCl₄) δ 6.83 (m, 1H, H-1), 6.63 (s, 2H, ArH), 5.85 (m, 1H, H-2), 3.80 (s, 6H, OMe), 2.1–2.7 (m, 4H, H-3,4)]. Vilsmeier formylation of (6) (POCl₃, N,N-dimethylformamide, 80°C, 4 h) gave the aldehyde (7) (m.p. 91–92°C). Grignard reaction on (7) (MeMgI, Et₂O, r.t., 1 h, N₂) afforded the (±)-2-(1-hydroxyethyl)-5,8-dimethoxy-3,4-dihydronaphthalene (m.p. 78–79°C; lit.⁸ m.p. 78–79°C).

Kinetic resolution of (±)-(8) was carried out at –55 to –50°C by treating (8) (1 mol. equiv.) in CH₂Cl₂ sequentially with titanium tetrakisopropoxide (TIP), (+)-di-isopropyltartrate [L-(+)-DIPT], and t-butylhydroperoxide (TBHP) in 1:1:0.6 molar ratio. The progress of the reaction was monitored by titrating the concentration of TBHP. After completion of the reaction (10 h), the reaction was quenched with aqueous acetone maintained at –50°C. Usual work up⁵ gave a mixture of two products (9) and (8b) which was directly subjected to reduction [LiAlH₄, tetrahydrofuran (THF), r.t., 4 h] followed by chromatographic separation (silica gel, benzene-acetone) to give R-(-)-(8b) (38% yield, m.p. 88–89°C, [α]_D²⁰ + 20.3° (c 0.5, EtOH)) and R-(-)-2-(S-1-hydroxyethyl)-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (-)-(10) (40% yield, m.p. 154–155°C, [α]_D²⁰ –49.4° (c 0.5, EtOH); lit.^{4c} m.p. 154–155°C, [α]_D²⁰ –49.7° (c 0.50, EtOH)). The undesired antipode (+)-(8b) was inverted⁹ by reacting with triphenylphosphine, diethyl azodicarboxylate, and benzoic acid in THF to give the benzoate of (-)-(8a). Hydrolysis (NaOMe, MeOH, r.t., 5 h) followed by purification (silica gel, hexane-acetone) afforded (-)-(8a) (70% yield, m.p. 86–88°C, [α]_D²⁰ –18.6° (c 0.5, EtOH)). Epimerization of (-)-(8a) [CH₂Cl₂, –55 to –50°C TIP, L-(+)-DIPT, TBHP, N₂] followed by reduction with LiAlH₄ gave (-)-(10) (83% yield, m.p. 152–154°C, [α]_D²⁰ –47.6° (c 0.5, EtOH)).

Oxidation of (-)-(10) with Fetizon's reagent¹⁰ (AgCO₂ celite) gave R-(-)-(3) (m.p. 128–129°C, [α]_D²⁰ –48.8° (c CHCl₃); lit.^{4b} m.p. 130–132°C, [α]_D²⁰ –50° (c 1, CHCl₃)). Fusion of R-(-)-(3) with phthalic anhydride in an intimate mixture of AlCl₃-NaCl (5:1) at 180°C (2 min) and usual work up gave (-)-4-demethoxy-7-deoxydaunomycinone (11) (m.p. 227–228°C, [α]_D²⁰ –84°C (c 0.1, CHCl₃); lit.¹¹ m.p. 228–230°C, [α]_D²⁰ –87° (c 0.1, CHCl₃)).

As the conversion of (11) into (1b)¹² and subsequently into (2b) by convenient methods¹¹ has already been described, we consider that our approach constitutes a practical total synthesis of optically active (2b).

[†] We are thankful to our colleagues, Jaweed and Sathaye for making available large amounts of this product. After completion of this work, a similar approach has been made use of by R. A. Russell, G. W. Collin, P. S. Gee, and R. N. Warrener, *J. Chem. Soc., Chem. Commun.*, 1983, 994.

All the new compounds gave satisfactory elemental and spectral analyses.

J. CHEM. SOC., CHEM. COMMUN., 1984.

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Received, 29th December 1983; Com. 1692

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

Young S. Rho,^{*} Hyun Kyoung Ko, Wan-Joong Kim, Dong Jin Yoo,[†] and Heun Soo Kang[‡]

Department of Chemistry, Chonbuk National University, Chonju 561-756, Korea

[†]Department of Chemistry, Seonam University, Namwon 590-711, Korea

[‡]Metabolic Engineering Laboratories Co., Ltd., 28 Yongon-Dong, Chongno-Gu, Seoul 110-799, Korea

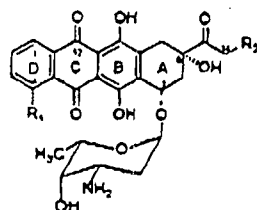
Received April 20, 2000

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 (daunorubicin) **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.¹⁻⁶ 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 relationship⁵ have been synthesized recently.^{6,7,8a,8c} In more recent papers, we have also reported the successful synthesis of various anthracycline derivatives.^{8a-8c}

Herein, we describe the total synthesis of a new 7-deoxyidarubicinone derivative **21**, a potential prodrug⁹ of anthracycline including an ester linkage of 14-OH in idarubicinone with a butyric acid residue. Additionally, we wish to describe the synthetic studies on an AB-synthon **14** necessary for the synthesis of the aglycon.

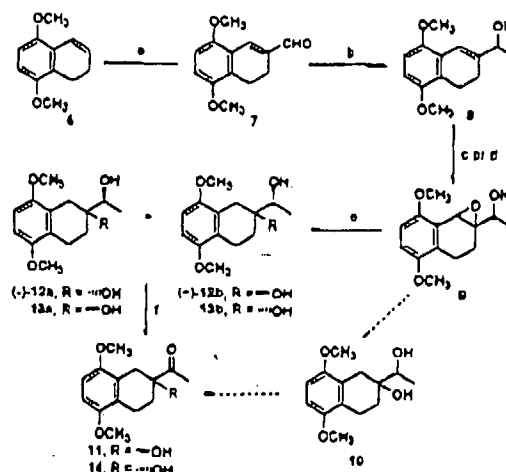


1. Adriamycin $R_1 = \text{OMe}, R_2 = \text{OH}$
 2. Daunorubicin $R_1 = \text{OMe}, R_2 = \text{H}$
 3. Carminomycin $R_1 = R_2 = \text{OH}$
 4. 4-Demethoxyadriamycin $R_1 = \text{H}, R_2 = \text{OH}$
 5. Idarubicin $R_1 = R_2 = \text{H}$

Figure 1. Some Daunorubicin Derivatives.

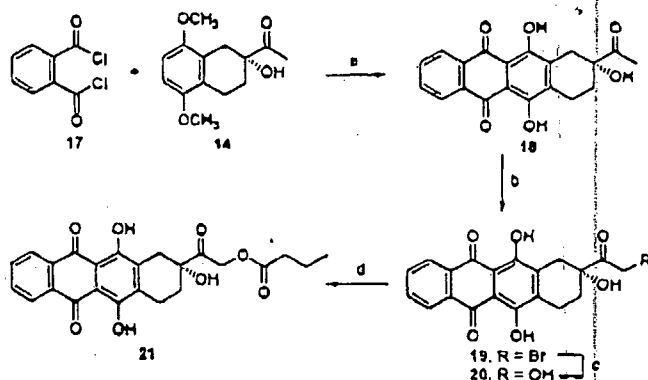
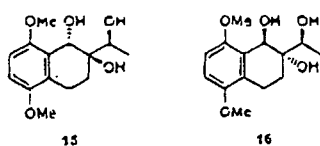
Results and Discussion

In the previous reports, we frequently used the Michael type reaction or the Friedel-Crafts acylation for the effective construction of tetracyclic skeleton in anthracycline.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 reagent¹² 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, $\text{VO}(\text{acac})_3$, PhH, rt.; Method B) (+)-DIPT, $\text{Ti}(\text{O}i\text{Pr})_4$, *t*-BuOOH, CH_2Cl_2 , $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$. (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,3d} The epoxidation of ($\pm$)-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.*¹² The epoxidation of the racemic allylic alcohol ($\pm$)-8 using Terashima method followed by reductive cleavage of the unstable epoxide ($\pm$)-9 was found to give the intermediate ($\pm$)-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 diastereomeric mixture of ($\pm$)-12/13 in 45% yield based on ($\pm$)-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 diastereomeric mixture of (($\pm$)-12/13) in ether afforded the major diastereomer (($\pm$)-12, 39%) in a pure state. The crude diastereomeric mixture (($\pm$)-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 ¹³C 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 (2*R*)-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 D₂O; (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(O*i*Pr)₄), and *tert*-butyl hydroperoxide at -78 °C.¹⁴ Optically pure (2*R*)-(-)-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



Scheme 2. (a) AlCl₃, PhNO₂, 80-100 °C. (b) PHT, THF, rt, 24 hrs. (c) 1% NaOH, Me₂CO, reflux. (d) BuCO₂H, DCC, DMF, rt.

side products as described above. Oxidation of ($\pm$)-12 or (-)-12a with Fetizon reagent¹⁵ in benzene afforded ($\pm$)-11 and (-)-14 in 90% and 78% yields, respectively. The physical and spectral properties of ($\pm$)-11 or (-)-14 were identical in all respects with the literature.^{8b,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-deoxydaurubicinone. 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 THF¹⁷ gave 19 in 90% yield. Hydrolysis of 19 with 1% NaOH in refluxing acetone gave mainly 20 in 53% yield. The esterification¹⁹ 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,^{8b-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 procedure²⁰ 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 ¹³C 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 $92-94^\circ\text{C}$; $^1\text{H-NMR}$ (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); $^{13}\text{C-NMR}$ (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.

($\pm$)-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 ; $^1\text{H-NMR}$ (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); $^{13}\text{C-NMR}$ (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 ($\pm$)-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.

(1 S^*)-1-[(1aR*,7bR*)-4,7-Dimethoxy-1a,2,3,7b-tetrahydronaphtho[1,2-b]oxiren-1-yl]-1-ethanol (($\pm$)-9). *tert*-Butyl hydroperoxide (0.46 mL, 6.0 M solution in decane, 2.77 mmol) was added to a mixture of ($\pm$)-**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 (($\pm$)-12) and Its Isomer (($\pm$)-13) from ($\pm$)-9. A solution of above crude ($\pm$)-**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 $\rightarrow$ 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 ($\pm$)-**12/13** (mp $142-148^\circ\text{C}$) was not carried out throughout purification, this sample should consist of the two diastereomers 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 ($\pm$)-12 and 27.3 (C_1 or C_4), 33.1 (C_4 or C_1) for ($\pm$)-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 ($\pm$)-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 ($\text{M}^+ - \text{H}_2\text{O}$), 207 (100), 189 (38), 175.

(1 S^* ,2 R^*)-2-[(1 S^*)-1-Hydroxyethyl]-5,8-dimethoxy-1,2,3,4-tetrahydro-1,2-naphthalenediol (($\pm$)-15). Spectral data of ($\pm$)-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.

(1 R^* ,2 S^*)-2-[(1 S^*)-1-Hydroxyethyl]-5,8-dimethoxy-1,2,3,4-tetrahydro-1,2-naphthalenediol (($\pm$)-16). Spectral data of ($\pm$)-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.

(2 R)-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 ($\pm$)-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, $[\alpha]_{\text{D}}^{20}$ -36.7° (c = 0.9, CH_3OH). (lit.^{13b} $[\alpha]_{\text{D}}^{20}$ -49.7° (c = 0.5, ethanol), lit.^{14a} $[\alpha]_{\text{D}}^{20}$ -34.3° (c = 1.2)).

1-[2-Hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthalenyl]-1-ethanone (($\pm$)-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 ($\pm$)-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 ($\text{M}^+ - \text{H}_2\text{O}$), 207 (100). Those spectral properties were identical with those reported.^{8a,12a}

1-[(2 R)-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 reagent¹⁵ (3.64 g, 3.64 mmol) as described for the preparation of ($\pm$)-11 yielded 177 mg (78%) of optically pure (-)-14 after purification by crystallization in hexane: mp 128–130 °C; $[\alpha]_{\text{D}}^{20}$ -48.2° (c = 0.98, CHCl_3), (lit.^{13b} mp 127–128.5 °C, $[\alpha]_{\text{D}}^{20}$ -49.7° (c = 0.5, ethanol), lit.^{14a} 128–129 °C $[\alpha]_{\text{D}}^{20}$ -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.

(8 R)-8-(2-Bromoacetyl)-6,8,11-trihydroxy-5,7,8,9,10,12-hexahydro-5,12-naphthacenedione (19). 7-Deoxyidarubicinone (-)-18 ($[\alpha]_{\text{D}}^{20}$ -84.4° (c = 0.1, CHCl_3), 97% ee, lit.^{13b} $[\alpha]_{\text{D}}^{20}$ -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.

(8 R)-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; $[\alpha]_{\text{D}}^{20}$ +49.9° (c = 0.004, CH_3OH); ^1H -NMR ($\text{DMSO}-d_6$) 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, $2 \times \text{CH}_2$), 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 ($\text{M}^+ - \text{H}_2\text{O}$), 310, 292.

2-Oxo-2-[(2 R)-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/ethyl-acetate = 3/1) gave **21** (0.27 g, 90.6%) as a red solid: mp 169–170 °C; ¹H-NMR (CDCl₃) δ 13.48 (s, 2H, ArOH), 8.33–8.34 (m, 2H, ArH), 7.81–7.84 (m, 2H, ArH), 5.1 (s, 2H, CH₂), 2.9–3.6 (m, 4H, 2 × CH₂), 2.45 (t, 2H, J = 7.32 Hz, CH₂), 1.93–2.34 (m, 2H, CH₂), 1.63–1.83 (m, 2H, J = 7.32 Hz, 7.81 Hz, CH₂), 1.01 (t, 3H, J = 7.32 Hz, 7.81 Hz, CH₃); IR (film) 3429, 2925, 2858, 1723, 1635, 1582, 1467, 1273, 1085, 1017 cm⁻¹; GC/MS (m/z) 438 (M⁺), 420 (M⁺-H₂O), 368.

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Preparation of dihydroxytetrahydronaphthacenedione derivatives as intermediates for anthracycline antibiotics

Tanno, Norihiko; Sato, Hiromi; Ishizumi, Kikuo

Sumitomo Pharmaceuticals Co., Ltd., Japan

Jpn. Kokai Tokkyo Koho, 9 pp.

CODEN: JKXXAF

Patent

Japanese

ICM " C07C050/38

ICS C07C046/02; C07C69/757; C07C102/00; C07C103/42; C07C103/78

C07H015-252

25-28 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)

Section cross-reference(s): 1, 26

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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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The title compds. [I; R1 = Ac, alkoxycarbonyl; R2 = OR3, NHCOR4 wherein R4 = H, hydroxy-protecting group; R4 = alkyl, haloalkyl, (halo)Ph], useful intermediates for anthracycline antibiotics, were prepd. by Friedel-Crafts reaction of Tetraline derivs. II with o-C6H4(COCl)2 in the presence of a Lewis acid. A mixt. of Tetraline deriv. 1-II (R1 = .beta.-Ac, R2 = .alpha.-NHAc), 100, o-C6H4(COCl)2 83.6, and AlCl3 229 mg in 5 mL (CH2Cl)2 was stirred for 3 h at room temp. to give 90.4% naphthacenedione deriv. 1 (R1 = .beta.-Ac, R2 = .alpha.-NHAc).

naphthacenedione dihydroxy prepn anthracycline intermediate; anthracycline antibiotic intermediate dihydroxytetrahydronaphthacene prepn; phthaloyl chloride Friedel Crafts naphthalene

Friedel Crafts reaction

(of tetrahydronaphthalene derivs., with phthaloyl chloride)

Antibiotics

(anthracycline, intermediates for, dihydroxytetrahydronaphthacenedione derivs. as)

112007-71-3

RL: RCT (Reactant)

(Friedel Crafts reaction of, with phthaloyl chloride)

41098-96-8 ***65818-79-3*** 71366-25-1 86264-62-2 112007-69-9

112007-70-2

RL: RCT (Reactant)

(Friedel Crafts reaction of, with phthaloyl dichloride)

88-95-9 Phthaloyl dichloride

RL: RCT (Reactant)

(Friedel Crafts reaction of, with tetrahydronaphthalene deriv.)

58957-92-9 64314-52-9 110267-81-7

RL: RCT (Reactant)

(intermediates for, dihydroxytetrahydronaphthacenedione derivs. as)

63229-48-1P 76527-50-9P 110267-87-3P 112007-67-7P 112007-68-8P

112067-29-5P

RL: SPN (Synthetic preparation); PREP (Preparation)

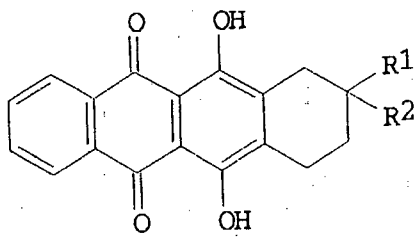
(prepn of, as intermediate for anthracycline antibiotics)

2007-70-2

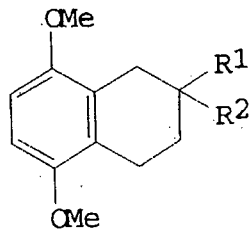
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Ethanone, 1-[2-(acetyloxy)-1,2,3,4-tetrahydro-5,8-dimethoxy-2-naphthalenyl]-, (R)- (9CI) (CA INDEX NAME)

STEREOSEARCH

C16 H20 O5

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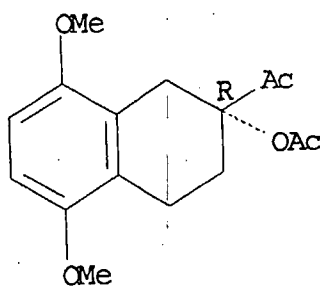
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Short-Step Asymmetric Syntheses of Anthracycline Antibiotics via Enantioselective Dihydroxylation by Osmium Tetroxide with a Chiral Diamine

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Abstract: Short-step asymmetric syntheses of (+)-7-dehydroxy-4-demethoxydaunomycinone **4** and (-)-9-deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyl-daunomycinone **5** were accomplished via enantioselective dihydroxylation by osmium tetroxide with chiral diamine **13**.

The clinical utility of the anthracycline antitumor antibiotics such as adriamycin (doxorubicin) **1** and daunomycin (daunorubicin) **2** is well established.¹ The 4-demethoxy series of compounds **4** and **5** have been developed as artificial anthracyclines of improved pharmacological profile. Since the biological activity of the anthracyclines is critically dependent on the chirality at C-9, extensive efforts have been devoted to asymmetric construction of this chiral center in the desired absolute configuration.^{2, 3}

We have reported the highly enantioselective dihydroxylation of olefins by osmium tetroxide with a chiral diamine **13**.⁴ Employing our system, diols of exceptionally high ee can be obtained from mono-, *trans*-di-, and trisubstituted olefins. The enantioface selection is shown by the general presentation in Fig. 2. Since both (+)- and (-)-**13** are readily accessible in optically pure form, this method provides a powerful tool for the synthesis of optically active alcohols in high-ee with desired absolute configuration from achiral olefins. In order to demonstrate the synthetic utility of our method, asymmetric syntheses of the anthracyclines were examined. We describe herein the details of successful short-step asymmetric syntheses of (+)-7-dehydroxy-4-demethoxydaunomycinone **4** and its hydroxymethyl analog (-)-9-deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyl-daunomycinone **5**.

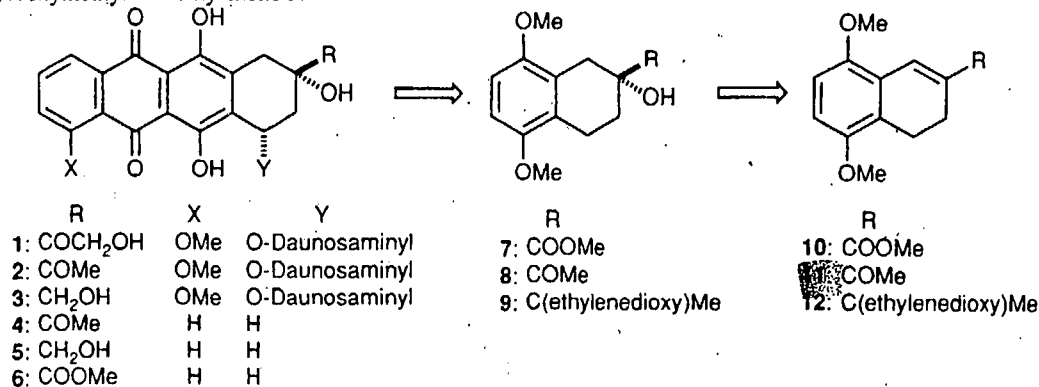


Fig. 1. Asymmetric Syntheses of Anthracyclines

Synthetic Plan

Optically active **7** and **8** are the most common key intermediates for the synthesis of anthracycline. It can be easily transformed into tetracycline skeleton by Friedel-Crafts condensation to afford **9** and **10** respectively. Our original plan for the asymmetric synthesis of **7** and **8** is to construct the stereocenters by the enantioselective dihydroxylation of **10** and **11** followed by reductive removal of benzylic hydroxyl groups. Applying the general presentation of the asymmetric dihydroxylation in Fig. 2, (-)-**13** should be employed as a chiral diamine in order to obtain **7** and **8** with desired absolute configuration.

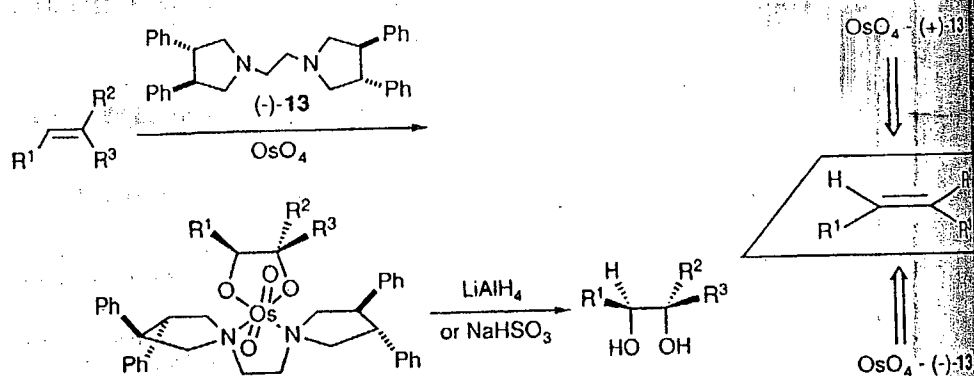


Fig. 2. Enantioselective Dihydroxylation of Olefins with OsO_4 with Chiral Diamine **13**

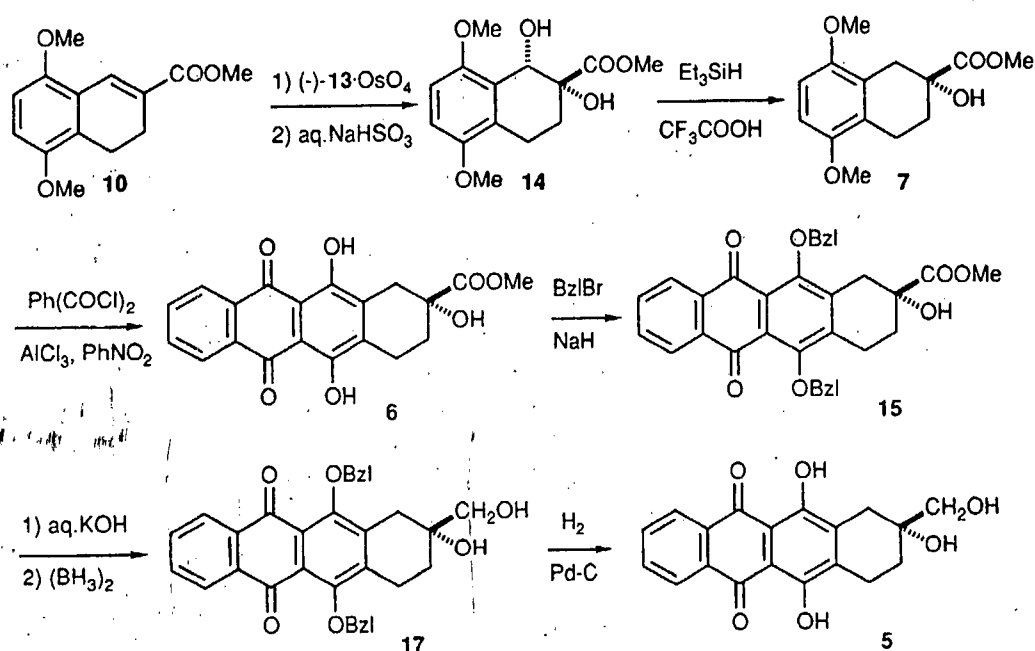
Enantioselective dihydroxylation of dihydronaphthalenes was studied with regard to the effect of substituents on efficiency in asymmetric induction. Treatment of dihydronaphthalene with osmium tetroxide (1.2 eq) in the presence of (-)-**13** (1.2 eq) in THF (0.01 M) at -110°C for 6 h and the following reductive workup of the resultant osmate with sodium bisulfite in refluxing aqueous THF, provided the corresponding diol. Optical purity and absolute configuration were determined by their conversion to **7** and **8**. As shown in Table 1, both **10** and **11** were oxidized in satisfactory ee with predicted absolute configuration (Run 1, 2). However, dihydronaphthalene with an ethylene acetal group provided the diol in only 36 % ee (Run 3). The results suggest that the substituents apparently affected the enantioselectivity. Since **7** and **8** are the important key intermediates in the synthesis of anthracyclines, this enantioselective dihydroxylation was proved to be effective in constructing the requisite chiral centers of anthracyclines. The successful results in the enantioselective dihydroxylation of **10** and **11** prompted us to accomplish the asymmetric syntheses of (-)-9-deacetyl-7-dehydroxy-4-demethoxydaunomycinone **5** from **10** and (+)-7-dehydroxy-4-demethoxydaunomycinone **4** from **11**.

Table 1. Enantioselective Dihydroxylation of Dihydronaphthalenes by OsO_4 with (-)-**13**

Run	Olefin	$[\alpha]_D^{25}(\text{CHCl}_3) (^\circ)$	ee (%)	yield (%)
1	10	-35.3	85	96
2	11	-17.6	82	96
3	12	-24.5	36	77

Synthesis of 9-Deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyl-daunomycinone 5

Total synthesis of (-)-9-deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyl-daunomycinone 5 was performed as shown in Scheme 1. The diol 14 obtained by enantioselective dihydroxylation was treated with triethylsilane in trifluoroacetic acid to provide 7 (85 % ee, $[\alpha]_D^{20}$ -29.5° (CHCl₃); lit.⁵ $[\alpha]_D^{20}$ -34.5° (CHCl₃)) in 94 % yield. Friedel-Crafts condensation was carried out with phthaloyl dichloride-aluminum chloride in nitrobenzene⁶ to provide tetracyclic core skeleton 6. Recrystallization from toluene gave practically optically pure 6 ($[\alpha]_D^{20}$ -57.2° (CHCl₃); lit.⁷ $[\alpha]_D^{25}$ -60.0° (CHCl₃)) in 68 %. This three-step procedure is the shortest route via asymmetric synthesis to obtain 6, which is a versatile key intermediate for the synthesis of anthracyclines with correct absolute configuration. We transformed 6 into 9-deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyl-daunomycinone 5. To overcome the solubility problem, 6 was benzylated with benzyl bromide to obtain 15. Reduction of ester was performed by successive hydrolysis and diborane reduction. Debenzylation by catalytic hydrogenation afforded optically pure 5 ($[\alpha]_D^{25}$ -31° (dioxane), lit.^{3k} ($[\alpha]_D^{25}$ -32° (dioxane)) in overall 22 % yield from 6.

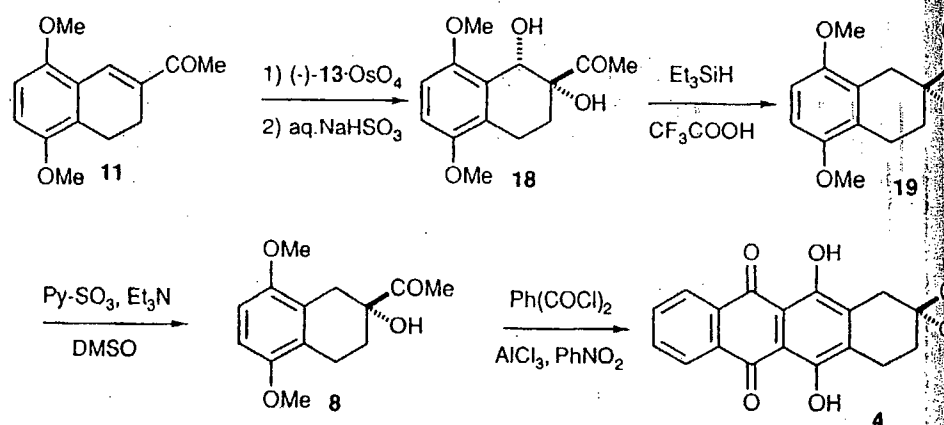


Scheme 1. Asymmetric Synthesis of 5

Synthesis of 7-Dehydroxy-4-demethoxydaunomycinone 4

Total synthesis of (+)-7-dehydroxy-4-demethoxydaunomycinone 4 was performed as shown in Scheme 2. The diol 18 obtained by enantioselective dihydroxylation was treated with triethylsilane in trifluoroacetic acid to provide 19 as a 3:4 diastereomeric mixture which was then oxidized with sulfur trioxide-pyridine complex and triethylamine in dimethylsulfoxide to afford 8 (82 % ee, $[\alpha]_D^{25}$ -39.3° (CHCl₃); lit.⁵ $[\alpha]_D^{25}$ -48.2° (CHCl₃)) in 68 % overall yield. Friedel-Crafts condensation with phthaloyl dichloride-aluminum chloride in nitrobenzene⁶ to provide the tetracyclic core skeleton 4. Recrystallization from benzene afforded 4 ($[\alpha]_D^{20}$ +150° (dioxane); lit.⁹

$[\alpha]_D^{20} +157^\circ$ (dioxane)) in optically pure form. The present four-step asymmetric synthesis in optically pure form constitutes the shortest route to 4. Elaboration of 4 to 4-demethoxydaunomycin is established technology.



Scheme 2. Asymmetric Synthesis of 4

Summary

The shortest asymmetric syntheses of (+)-7-dehydroxy-4-demethoxydaunomycinone 4 and (-)-9-dehydroxy-4-demethoxy-9-hydroxymethyl-daunomycinone 5 were accomplished via enantioselective dihydroxylation by osmium tetroxide with chiral diamine 13. These syntheses proved that enantioselective dihydroxylation mediated by the chiral diamine 13 is effective in constructing the requisite chiral center in target molecules.

Experimental Section

Melting points were measured using a Büchi 510 melting point apparatus and are not corrected. Optical rotations were taken with a JASCO DIP-370 digital polarimeter. IR spectra were taken with a JASCO infrared spectrometer and expressed in cm^{-1} . $^1\text{H-NMR}$ spectra were taken with a JEOL FX-100 spectrometer at 100 MHz. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. MS spectra were taken with a JEOL DX-300 mass spectrometer.

(1S,2R)-Methyl 1,2,3,4-Tetrahydro-1,2-dihydroxy-5,8-dimethoxynaphthalene-2-carboxylate (14)

To a cooled (-78°C) solution of the chiral diamine (-)-13 (80 mg, 0.17 mmol) in THF (6 ml) was added a solution of osmium tetroxide (40 mg, 0.16 mmol) in THF (3 ml). A solution of 10 (37 mg, 0.14 mmol) in THF (5 ml) was added to the bright wine-red solution above at -110°C and the whole was stirred for 6 h at this temperature. Sodium bisulfite (1.0 g) and water (2 ml) was added to the reaction mixture and the whole was stirred for 10 h under reflux. The reaction mixture was basified with NaHCO_3 and concentrated. The

was suspended in ethyl acetate (50 ml) and filtered through Celite pad. The water layer of the filtrate was extracted with ethyl acetate (20 ml x2) and combined organic layer was washed with brine and dried over Na_2SO_4 . Concentration and following purification by silica gel column chromatography (benzene-ethyl acetate, 10/1 to 1/1) gave chiral diamine **13** (77 mg, 96 %) and diol **14** (40 mg, 95 %) as a caramel of $[\alpha]_{\text{D}}^{25} -35.3^\circ$ ($c=0.80$, CHCl_3). IR (CHCl_3): 3550, 1740. $^1\text{H-NMR}$ (CDCl_3) δ : 2.0-2.3 (2H, m, CH_2), 2.8-3.0 (2H, m, CH_2), 3.7-3.9 (11H, m, OCH_3 , OH), 5.29 (1H, s, CH), 6.73 (2H, s, Ar). MS m/z : 282 (M^+). HRMS Calcd for $\text{C}_{14}\text{H}_{18}\text{O}_6$: 282.1100. Found: 282.1068.

(2R)-Methyl 1,2,3,4-Tetrahydro-2-hydroxy-5,8-dimethoxy-naphthalene-2-carboxylate (**7**)

A mixture of diol **14** (23 mg, 0.078 mmol), triethylsilane (0.016 ml, 0.093 mmol), and trifluoroacetic acid (0.4 ml) was stirred at 0°C for 20 min. Satd. NaHCO_3 (10 ml) and ethyl acetate (30 ml) was added to the mixture and the organic layer was washed with satd. NaHCO_3 and brine. After drying over Na_2SO_4 and concentration, the residue was purified by silica gel column chromatography (hexane-ethyl acetate, 20/1) to afford **7** (20.3 mg, 94 %) as a caramel of $[\alpha]_{\text{D}}^{20} -29.5^\circ$ ($c=2.03$, CHCl_3), (85 %ee, lit.⁵ $[\alpha]_{\text{D}}^{20} -34.5^\circ$ ($c=1.24$, CHCl_3)). IR (CHCl_3): 3550, 1730. $^1\text{H-NMR}$ (CDCl_3) δ : 1.9-2.1 (2H, m, CH_2), 2.7-3.0 (5H, m, CH_2 , OH), 3.76 (3H, s, CH_3O), 3.78 (3H, s, CH_3O), 3.82 (3H, s, CH_3O), 6.64 (2H, s, Ar). MS m/z : 267 (MH^+), 266 (M^+), 248 ($\text{M}^+ - \text{H}_2\text{O}$).

(2R)-Methyl 1,2,3,4,6,11-Hexahydro-2,5,12-trihydroxy-6,11-dioxonaphthacene-2-carboxylate (**6**)

To a solution of **7** ($[\alpha]_{\text{D}}^{20} -29.5^\circ$ ($c=2.03$, CHCl_3), 85 %ee, 10 mg, 0.038 mmol) in nitrobenzene (1 ml) was added a solution of aluminum chloride (10 mg, 0.075 mmol) in nitrobenzene (1 ml) and the mixture was stirred for 30 min at room temperature. Phthaloyl dichloride (7.6 mg, 0.037 mmol) was added to the resulting green solution and the whole was stirred at 100°C for 30 min. 0.2N oxalic acid (10 ml) and ethyl acetate (20 ml) were added to the resulting purple solution and the whole was filtered through Celite pad. The water layer was extracted with ethyl acetate (20 ml x3) and the combined organic layer was washed with satd. NaHCO_3 (20 ml x2), brine (20 ml). After drying over MgSO_4 , concentration followed by silica gel column chromatography (benzene-dichloromethane, 1/4) afforded **6** (11.0 mg, 80 %) as red prisms of mp $198-205^\circ\text{C}$. $[\alpha]_{\text{D}}^{20} -51.0^\circ$ ($c=0.10$, CHCl_3), (85 %ee). Recrystallization from toluene (0.1 ml) at -78°C gave red prisms (9.4 mg, 68 %) of mp $209-210^\circ\text{C}$. $[\alpha]_{\text{D}}^{20} -57.2^\circ$ ($c=0.10$, CHCl_3). [lit.⁷ mp $210.5-211.5^\circ\text{C}$, $[\alpha]_{\text{D}}^{25} -60.0^\circ$ ($c=0.10$, CHCl_3)]. IR (KBr): 1730, 1620, 1590. $^1\text{H-NMR}$ (CDCl_3) δ : 2.0-2.2 (2H, m, CH_2), 2.9-3.1 (5H, m, CH_2 , OH), 3.88 (3H, s, CH_3O), 7.8-7.9 (2H, m, Ar), 8.3-8.4 (2H, m, Ar), 13.49 (2H, s, ArOH). MS m/z : 368 (M^+).

(2R)-Methyl 5,12-Bis(phenylmethoxy)-1,2,3,4,6,11-hexahydro-2-hydroxy-6,11-dioxonaphthacene-2-carboxylate (**15**)

A suspension of NaH (60 % dispersion in oil, 25 mg, 0.62 mmol) in THF (1 ml) was added to a solution of **6** (100 mg, 0.27 mmol) in THF (100 ml) at -78°C under Ar atmosphere and allowed to stand at room temperature. Tetra-*n*-butylammonium iodide (220 mg, 0.60 mmol) and benzyl bromide (0.5 ml, 4.2 mmol) were added to the reaction mixture and the whole was stirred under reflux for 5 h. After adding 10 % HCl (20 ml), the whole was extracted with ethyl acetate (20 ml x3). The combined organic layer was washed with 10 % HCl (20 ml), satd. NaHCO_3 (20 ml), brine (20 ml) and dried over MgSO_4 . Purification by silica gel column

chromatography (benzene-dichloromethane, 1/0 to 1/4) followed by recrystallization from benzene (137 mg, 92 %) as yellow prisms of mp 191°C. $[\alpha]_{D}^{25} +25^{\circ}$ ($c=0.12$, CHCl_3). IR (CHCl_3): 1730. $^1\text{H-NMR}$ (CDCl_3) δ : 1.8-2.0 (2H, m, CH_2), 2.9-3.0 (5H, m, CH_2OH), 3.80 (3H, s, CH_3O), 5.03 (4H, 7.3-7.8 (12H, m, Ar), 8.2-8.3 (2H, m, Ar). MS m/z : 548 (M^+), 530 ($\text{M}^+-\text{H}_2\text{O}$). Anal. calcd for $\text{C}_{33}\text{H}_{26}\text{O}_7$: C, 74.44; H, 5.14. Found: C, 74.28; H, 5.10.

(2R)-5,12-Bis(phenylmethoxy)-1,2,3,4,6,11-hexahydro-2-hydroxy-6,11-dioxonaphthalene-1-carboxylic acid (16)

3 % KOH (0.45 ml, 0.24 mmol) was added to a solution of **15** (93 mg, 0.17 mmol) in THF-MeOH (20 ml) and the whole was stirred for 1 h. After adding 10 % HCl (5 ml), and the whole was extracted with ethyl acetate (20 ml x3) and washed with water (10 ml x3), brine (10 ml) and dried over MgSO_4 . Purification by silica gel column chromatography (dichloromethane-methanol, 8/1) afforded **16** (70 mg, 77 %) as a caramel. $[\alpha]_{D}^{27} +27^{\circ}$ ($c=0.55$, CHCl_3). IR (CHCl_3): 1670, 1720. $^1\text{H-NMR}$ (CDCl_3) δ : 1.8-2.1 (2H, m, CH_2), 2.7-3.1 (5H, m, CH_2OH), 5.00 (4H, s, CH_2), 6.1 (2H, brs, COOH , OH), 7.0-7.8 (12H, m, Ar), 8.0-8.2 (2H, m, Ar). MS m/z : 534 (M^+). HRMS Calcd for $\text{C}_{33}\text{H}_{26}\text{O}_7$: 534.1679. Found: 534.1631.

(8R)-6,11-Bis(phenylmethoxy)-7,8,9,10-tetrahydro-8-hydroxy-8-hydroxymethyl-5,12-naphthacenedione (17)

Diborane (1M in THF, 0.37 ml, 0.37 mmol) was added to a solution of **16** (20 mg, 0.037 mmol) in THF (2 ml) at 0°C and the reaction mixture was stirred for 4 h at room temperature. 10 % HCl (20 ml) was added to the mixture and the whole was stirred for 1 h at room temperature. After extraction with ethyl acetate (20 ml x3), the organic layer was washed with 10 % HCl (20 ml), satd. NaHCO_3 (20 ml), brine (20 ml) and dried over Na_2SO_4 . Purification by silica gel column chromatography (benzene-ethyl acetate, 3/1) afforded **17** (10 mg, 50 %) as yellow prisms of mp 170°C. $[\alpha]_{D}^{25} -37^{\circ}$ ($c=0.32$, CHCl_3). IR (CHCl_3): 1670, 1400. $^1\text{H-NMR}$ (CDCl_3) δ : 1.5-2.0 (2H, m, CH_2), 2.7-3.0 (5H, m, CH_2OH), 3.44 (1H, s, OH), 5.04 (4H, s, CH_2), 7.3-7.6 (12H, m, Ar), 7.7-7.8 (2H, m, Ar), 8.2-8.3 (2H, m, Ar). MS m/z : 521 (MH^+), 520 (M^+), 502 ($\text{M}^+-\text{H}_2\text{O}$). Calcd for $\text{C}_{33}\text{H}_{28}\text{O}_6$: 520.1886. Found: 520.1906.

(8R)-7,8,9,10-Tetrahydro-6,8,11-trihydroxy-8-hydroxymethyl-5,12-naphthacenedione-1,2-diacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyl-daunomycinone (5)

A mixture of **17** (5 mg) and palladium on carbon (10 %, 2 mg) in dioxane-ethanol (1:1, 2 ml) was stirred for 12 h at room temperature under hydrogen atmosphere. Filtration followed by purification with silica gel column chromatography (dichloromethane-acetone, 4:1) afforded **5** (2 mg, 61 %) as red prisms of mp 236°C. $[\alpha]_{D}^{25} -31^{\circ}$ ($c=0.20$, dioxane). (lit.^{3k} mp 235-238°C, $[\alpha]_{D}^{25} -32^{\circ}$ ($c=0.06$, dioxane).) IR (dioxane) ν : 1590. $^1\text{H-NMR}$ (pyridine- d_5) δ : 2.0-2.5 (2H, m, CH_2), 3.0-4.0 (8H, m, CH_2OH , singlet at 4.02 (2H, m, Ar), 8.3-8.4 (2H, m, Ar). MS m/z : 340 (M^+), 309 ($\text{M}^+-\text{CH}_2\text{OH}$), 291 ($\text{M}^+-\text{CH}_2\text{OH}-\text{H}_2\text{O}$). Calcd for $\text{C}_{19}\text{H}_{16}\text{O}_6$: 340.0947. Found: 340.0959.

(1R,2R)-2-Acetyl-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalene-1,2-diol (18)

To a cooled (-78°C) solution of the chiral diamine (-)-**13** (98 mg, 0.21 mmol) in THF (10 ml) was added a solution of osmium tetroxide (48 mg, 0.19 mmol) in THF (1 ml). A solution of **11** (40 mg, 0.17 mmol)

(1 ml) was added to the bright wine-red solution above at -110°C and the whole was stirred for 6 h at the same temperature. Sodium bisulfite (0.20 g) and water (4 ml) was added to the reaction mixture and the whole was stirred for 14 h under reflux. The reaction mixture was basified with NaHCO_3 and concentrated. The residue was suspended in ethyl acetate (50 ml) and filtered through Celite pad. The water layer of the filtrate was extracted with ethyl acetate (20 ml x2) and combined organic layer was washed with brine and dried over Na_2SO_4 . Concentration and the following purification by silica gel column chromatography (benzene-ethyl acetate, 10/1 to 1/1) gave chiral diamine **13** (94 mg, 96 %) and diol **18** (44 mg, 96 %) as a caramel of $[\alpha]_{\text{D}}^{25}$ 17.6° ($c=1.10$, CHCl_3). IR (CHCl_3): 1710, 1600. $^1\text{H-NMR}$ (CDCl_3) δ : 1.7-2.1 (2H, m, CH_2), 2.39 (3H, s, CH_3CO), 3.7-3.9 (2H, m, CH_2), 3.8-4.0 (8H, m, CH_3O , and OH), 5.31 (1H, s, CH), 6.72 (2H, s, Ar). MS m/z : 267 (MH^+), 266 (M^+). HRMS Calcd for $\text{C}_{14}\text{H}_{18}\text{O}_5$: 266.1154. Found: 266.1174.

(2R,1'R) and (2R,1'S)-1,2,3,4-Tetrahydro-2-(1-hydroxyethyl)-5,8-dimethoxynaphthalen-2-ol (19)

A mixture of diol **18** (17 mg, 0.064 mmol), triethylsilane (0.14 ml, 0.088 mmol), and trifluoroacetic acid (0.7 ml) was stirred at -20°C for 12 h. Satd. NaHCO_3 (10 ml) and ethyl acetate was added to the mixture and the organic layer was washed with satd. NaHCO_3 and brine. After drying over Na_2SO_4 and concentration, the residue was purified by silica gel column chromatography (hexane-ethyl acetate, 3/1) to afford **19** (12.5 mg, 78 %) as a caramel. IR (CHCl_3): 3400-3450, 1600, 1480. $^1\text{H-NMR}$ (CDCl_3) δ : 1.25 (isomer: 1.27) (3H, d, $J=7\text{Hz}$, CH_3), 1.5-2.0 (5H, m, CH, CH_2 , OH), 2.5-2.9 (4H, m, CH_2), 3.77 (3H, s, CH_3O), 3.78 (3H, s, CH_3O), 6.63 (2H, s, Ar). MS m/z : 253 (MH^+), 252 (M^+). $^1\text{H-NMR}$ showed the ratio of isomers was 3:4.

(2R)-2-Acetyl-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalen-2-ol (8)

Triethylamine (0.32 ml, 2.3 mmol) and sulfur trioxide-pyridine complex (130 mg, 0.82 mmol) were added to a solution of diol **19** (20 mg, 0.080 mmol) in DMSO (0.2 ml). After adding 10 % HCl (10 ml) and ethyl acetate (50 ml), the organic layer was washed with 10 % HCl (10 ml), satd. NaHCO_3 (10 ml x2), brine and dried over Na_2SO_4 . Concentration followed by purification by silica gel column chromatography (benzene-ethyl acetate, 7/1) afforded **8** as colorless prisms (8.8 mg, 87 %) of mp $122-125^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{25}$ -39.3° ($c=0.88$, CHCl_3) (82 % ee, lit.⁵ mp $128-129^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{25}$ -48.2° ($c=0.982$, CHCl_3)). IR (CHCl_3): 1710, 1490. $^1\text{H-NMR}$ (CDCl_3) δ : 1.8-2.1 (2H, m, CH_2), 2.30 (3H, s, CH_3CO), 3.61 (1H, s, OH), 3.79 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 6.71 (2H, s, Ar). MS m/z : 251 (MH^+), 250 (M^+), 232 ($\text{M}^+-\text{H}_2\text{O}$).

3,4-Dihydro-5,8-dimethoxy-2-(1-methyl-2,5-dioxan-1-yl)naphthalene (12)

A mixture of ketone **8** (36 mg, 0.16 mmol), ethylene glycol (96 mg, 1.5 mmol) and p-toluenesulfonic acid (3 mg, 0.016 mmol) in benzene (15 ml) was stirred under reflux azeotropically for 12 h. The reaction mixture was diluted with ethyl acetate (40 ml) and washed with satd. NaHCO_3 (10 ml), water (20 ml x2), brine (20 ml) and dried over MgSO_4 . Concentration followed by purification by silica gel column chromatography (benzene) afforded **12** as a caramel (47 mg, 99 %). IR (CHCl_3): 1660, 1600. $^1\text{H-NMR}$ (CDCl_3) δ : 1.54 (3H, s, CH_3), 2.1-2.3 (2H, m, CH_2), 3.78 (6H, s, OCH_3), 3.8-4.0 (4H, m, CH_2), 6.68 (2H, s, Ar), 6.98 (1H, s, CH). MS m/z : 276 (M^+). Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_4$: 276.1361. Found: 276.1384.

(1S,2R)-3,4-Dihydro-5,8-dimethoxy-2-(1-methyl-2,5-dioxan-1-yl)naphthalene-1,2-diol (20)

To a cooled (-78°C) solution of the chiral diamine (-)-**13** (60 mg, 0.13 mmol) in THF (8 ml) was added a solution of osmium tetroxide (29 mg, 0.12 mmol) in THF (1 ml). A solution of **12** (29 mg, 0.11 mmol) in THF (2 ml) was added to the bright wine-red solution above at -110°C and the whole was stirred for 2 h at the same temperature and then 4 h at -78°C . Sodium bisulfite (1.0 g) and water (5 ml) was added to the reaction mixture and the whole was stirred for 12 h under reflux. The reaction mixture was basified with NaHCO_3 and concentrated. The residue was suspended in ethyl acetate (30 ml) and filtered through Celite pad. The water layer of the filtrate was extracted with ethyl acetate (10 ml x2) and combined organic layer was washed with brine and dried over Na_2SO_4 . Concentrated and purification by silica gel column chromatography (dichloromethane-ethyl acetate, 6/1) afforded diol **20** (25 mg, 77 %) as a caramel of $[\alpha]_{\text{D}}^{25} -24.5^{\circ}$ ($c=1.24$, CHCl_3). IR (CHCl_3): 3500, 1600. $^1\text{H-NMR}$ (CDCl_3) δ : 1.46 (3H, s, CH_3), 2.1-2.3 (2H, m, CH_2), 2.7-2.9 (2H, m, CH_2 , OH), 3.56 (1H, s, OH), 3.77 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.02 (4H, s, CH_2CH_2), 5.14 (1H, s, CH), 6.70 (2H, s, Ar). MS m/z : 311 (MH^+), 310 (M^+). HRMS Calcd for $\text{C}_{16}\text{H}_{22}\text{O}_6$: 310.1415. Found: 310.1410.

(2R)-2-Acetyl-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalen-2-ol (18) from ketal 20

A solution of ketal **20** (19 mg) and 10 % HCl (0.4 ml) in THF (4 ml) was stirred for 2 d at room temperature. The mixture was diluted with ethyl acetate (90 ml) and washed with satd. NaHCO_3 (10 ml), brine (20 ml) and dried over Na_2SO_4 . Concentration followed by silica gel column chromatography (benzene-ethyl acetate, 10/1) gave **18** (14.3 mg, 88 %) as a caramel of $[\alpha]_{\text{D}}^{25} -7.7^{\circ}$ ($c=1.43$, CHCl_3), (36 %ee based on the optical rotation of Table 1 Run 2).

(8R)-8-Acetyl-7,8,9,10-tetrahydro-6,11,8-trihydroxy-5,12-naphthacenedione (4-Demethoxy-7-dehydroxydaunomycinone 4)

To a solution of **8** ($[\alpha]_{\text{D}}^{25} -39.3^{\circ}$ ($c=0.880$, CHCl_3), 82 % ee, 15 mg, 0.060 mmol) in nitrobenzene (2 ml) was added a solution of aluminum chloride (16 mg, 0.12 mmol) in nitrobenzene (0.5 ml) and the mixture was stirred for 30 min at room temperature. Phthaloyl dichloride (12 mg, 0.060 mmol) was added to the resulting orange solution and the whole was stirred at 100°C for 1 h. 0.2N oxalic acid (10 ml) and chloroform (30 ml) were added to the resulting purple solution and the whole was filtered through celite pad. The water layer was extracted with chloroform (10 ml x3) and the combined organic layer was washed with satd. NaHCO_3 (20 ml x2), brine (20 ml). After drying over MgSO_4 , concentration followed by silica gel column chromatography (benzene-dichloromethane, 1/3) afforded **4** (16 mg, 76 %) as red prisms of mp $209-215^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{20} -73.0^{\circ}$ ($c=0.14$, CHCl_3), (81 %ee). Recrystallization from benzene (0.5 ml) gave red prisms (9.0 mg, 53 %) of mp $217-218^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{20} -86.2^{\circ}$ ($c=0.10$, CHCl_3), ((96 %ee, lit.⁹ mp $218-219.5^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{25} -90.6^{\circ}$ ($c=0.106$, CHCl_3)). IR (KBr): 3400, 1700, 1620. $^1\text{H-NMR}$ (CDCl_3) δ : 1.7-2.2 (2H, m, CH_2), 2.39 (3H, s, OCH_3), 2.8-3.5 (4H, m, CH_2), 3.80 (1H, s, OH), 7.7-7.9 (2H, m, Ar), 8.2-8.5 (2H, m, Ar), 13.49 (2H, s, ArOH). MS m/z : 352 (M^+), 309 ($\text{M}^+ - \text{COCH}_3$).

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10816

M. NAKAJIMA *et al.*

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Total Synthesis of (±)-4-Demethoxydaunomycinone†

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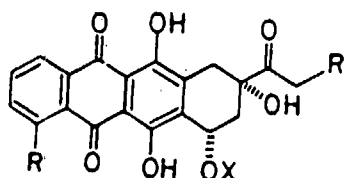
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2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (4), the key synthon for the total synthesis of various antitumor anthracyclines, has been prepared either from 1,4-dimethoxynaphthalene and making use of metal-ammonia reduction or from benzoquinone and going through Diels-Alder reaction with 1,3-butadiene. 4 is then converted into (±)-4-demethoxydaunomycinone (3b).

In the field of anthracyclines as anticancer agents¹, the synthetic analogue, 4-demethoxydaunomycin (3a) has assumed considerable clinical importance as it is found to be 8 to 10 times more effective than naturally occurring daunomycin (1a) or adriamycin (2a)². Further, 3a is orally active³. As there is no possibility of obtaining 3a by fermentation, and many suitable methods for the synthesis of L-daunosamine including two of our approaches⁴ either starting from glucose or glucosamine and its coupling to the aglycone (4-demethoxydaunomycinone, 3b), have already been accomplished⁵, our main efforts have been directed towards evolving a convenient synthesis of the aglycone (3b). Amongst several approaches⁶ towards the synthesis of both daunomycinone (1b) and 3b, the method first employed by Wong *et al.*⁷ for the assemblage of the tetracyclic system by AB + CD

coupling seems to be most promising. It involves the preparation of 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (4) representing the final AB rings and its condensation by acylation with phthalic anhydride corresponds to CD rings in the tetracyclic system. Various methods have since been reported for the synthesis of 4 which can be smoothly converted into 4-demethoxy-7-deoxydaunomycinone (5)⁸. We now report an efficient and a much simpler approach towards 4 employing easily accessible organic intermediates. Precise experimental procedures for the successful elaboration of such products have been outlined in view of their interesting application for the synthesis of other anthracyclines.

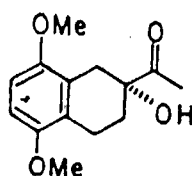
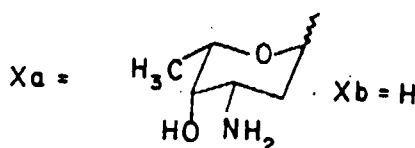
Our first approach for the synthesis of 4 was from 1,4-dimethoxynaphthalene (6) and used of metal-ammonia reduction as the key step as depicted in



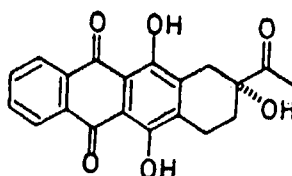
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2 : R = OMe, R' = OH

3 : R = R' = H

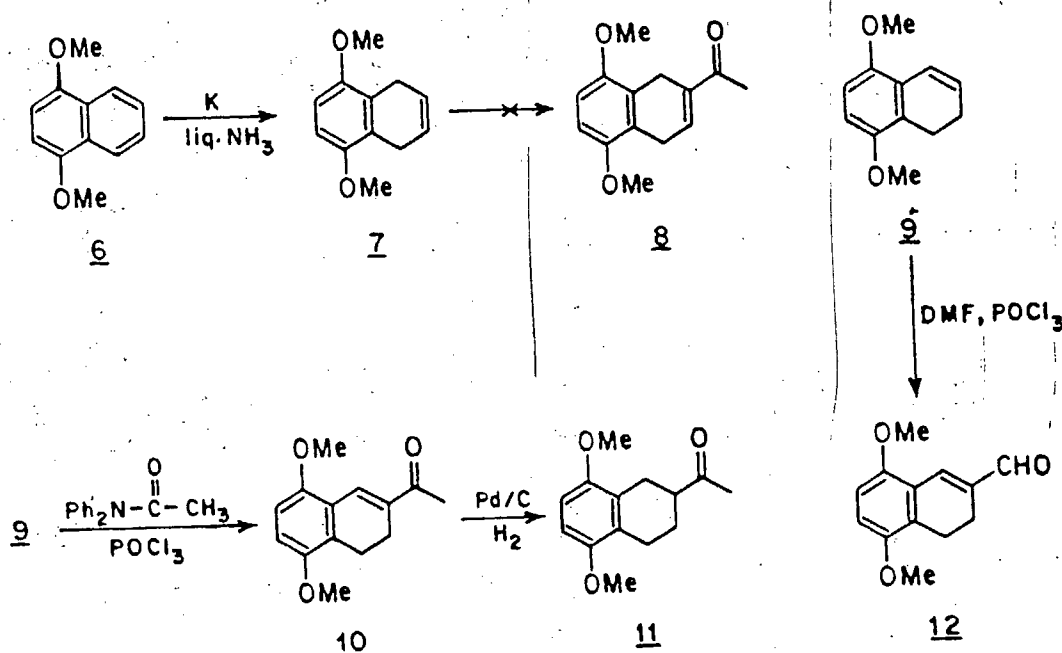


4



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†NCL Communication No. 3687



Scheme 1

Scheme 1. Thus metal-ammonia reduction of 6 either with lithium in liquid ammonia or lithium in ethylenediamine or potassium in ethylenediamine resulted in the recovery of starting material (in different gram atom equivalents). However, 6 on reduction with potassium in liquid ammonia, followed by quenching the reaction mixture with ethanol afforded 5,8-dimethoxy-1,4-dihydronaphthalene (7).

The various attempts to acylate the ethylenic double bond in 7 to achieve 8 (e.g. acetic anhydride-BF₃-etherate, acetic anhydride-AlCl₃, acetyl chloride-SnCl₄, acetyl chloride-ZnCl₂, acetic acid-PPA etc.) which could then be easily epoxidised and reductively opened to give the desired 4, resulted in a complex mixture. In view of this it was decided to isomerise the olefinic bond in 7 to the conjugated position as in 9 in the hope that 9 will be more prone to such acylation reactions. 7 on treatment with potassium *t*-butoxide in dimethyl sulfoxide under nitrogen atmosphere at room temperature resulted in the formation of 5,8-dimethoxy-3,4-dihydronaphthalene (9) in almost quantitative yield. After several unsuccessful attempts to acylate 9, it was found that using N,N-diphenylacetamide-phosphorous oxychloride in chloroform resulted in the formation of 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (10) in 10% yield. Attempts to improve the yield of 10 by varying the conditions of Vilsmeier-Haack reaction were unsuccessful. Catalytic hydrogenation of 10 using 5% Pd/C resulted in the formation of 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (11) in 90% yield. Tertiary hydroxylation at C-2 position in 11 was achieved by treating 11 with potassium *t*-butoxide in *t*-butanol and bubbling oxygen followed by reduction

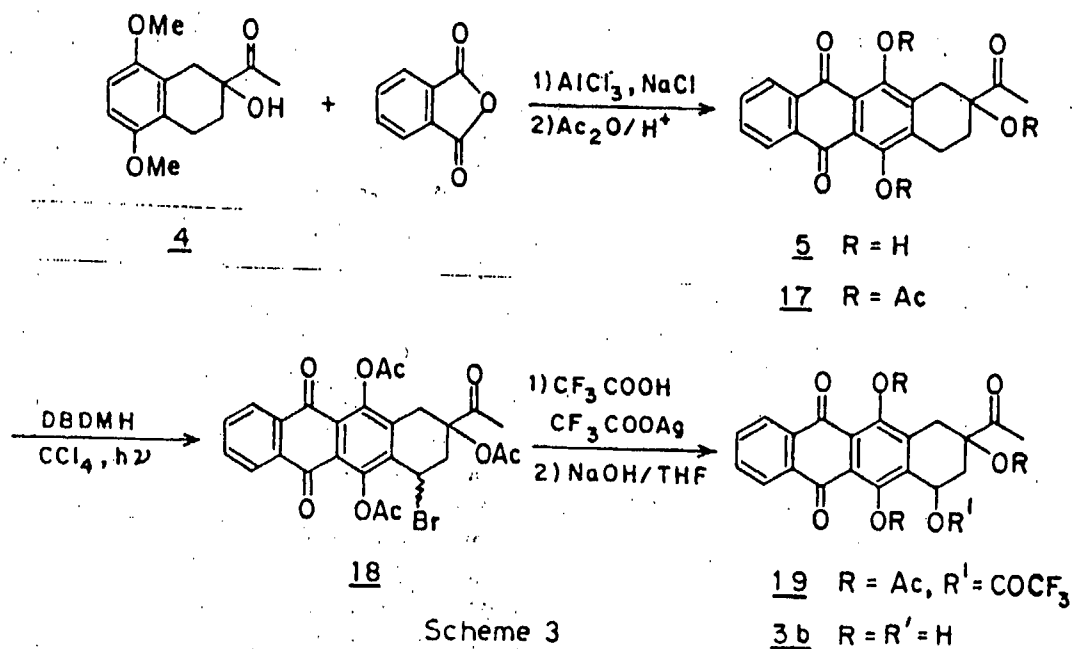
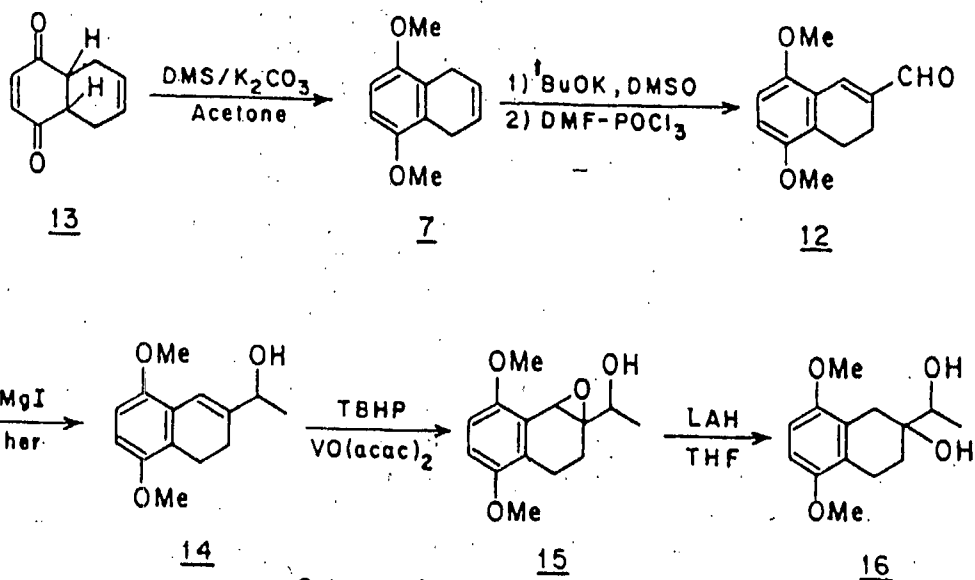
with zinc/acetic acid⁷ to give the desired ($\pm$)-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (4) in 60% yield. It was evident that this approach is suitable to obtain 4 in reasonable quantity.

Earlier it was demonstrated⁸ that 9 under formylation under Vilsmeier-Haack conditions (dimethylformamide and POCl₃) to give 2-formyl-5,8-dimethoxy-3,4-dihydronaphthalene (12) which can be smoothly transformed to 4 by appropriate reactions. However, 12 itself was obtainable through multistep operations⁹. This approach, therefore, was not attempted.

In yet another approach (Scheme 2) Diels-Alder reaction of *p*-benzoquinone with 1,3-butadiene in glacial acetic acid at room temperature afforded adduct (13) in 90% yield. Methylation of 13 (Me₂CO-K₂CO₃-acetone method) afforded 5,8-dimethoxy-3,4-dihydronaphthalene (7) in 90% yield. This product was identical in all respects with that obtained by metal-ammonia reduction on 1,4-dimethoxynaphthalene. Base-catalysed isomerisation of 7 with potassium *t*-butoxide in DMSO afforded 9 in quantitative yield. Vilsmeier-Haack formylation (POCl₃-DMF, 80°C) gave 12 in more than 90% yield. Grignard reaction of 12 with methylmagnesium iodide in ether afforded 2-methyl-5,8-dimethoxy-3,4-dihydronaphthalene (14) in 66% overall yield.

Epoxidation of 14 using *t*-butyl hydroperoxide and vanadyl acetylacetonate in benzene at room temperature followed by reduction with lithium aluminium hydride in tetrahydrofuran at room temperature afforded the vicinal diol (16). For oxidation¹⁰ of ($\pm$)-16 resulted in the formation of 4 in very good yield. Further conversion of ($\pm$)-

RAMA RAO *et al.*: SYNTHESIS OF (±)-DEMETHOXYDAUNOMYCINONE



demethoxydaunomycinone (3b) was achieved as depicted in Scheme 3.

Compound (4) was converted into 4-demethoxy-7-deoxydaunomycinone (5) in 70% yield^{8a}. The hydroxylation of the C-7 benzylic position in 5 was achieved by literature procedure via bromination of the corresponding triacetate (17), using 1,3-dibromo-5,5-dimethylhydantoin¹¹. Treatment of the bromo compound (18) with silver trifluoroacetate in trifluoroacetic acid at room temperature gave 19 in 30% yield. Various modifications made at this stage did not improve the yield of 19. Hydrolysis of 19 with sodium hydroxide in THF yielded (±)-4-demethoxydaunomycinone (3b) in 40% yield. The PMR and other spectral data of 3b are in complete agreement with the earlier reported data¹¹.

Thus the total synthesis of (±)-3b was accomplished by a practical and preparatively useful method.

Experimental Procedure

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer model 683 spectrophotometer and PMR spectra on either Varian T-60 or Varian FT-80 spectrometer (chemical shifts are given in δ scale) using TMS as an internal standard. Mass spectra were recorded on a CEC 21-110B mass spectrometer.

Analytical thin layer chromatography (TLC) was performed on (15×4 cm) glass plates with Acme's silica gel and visualisation of the spots was achieved by exposure to iodine vapour. For column chromatography Acme's silica gel (60-120 mesh) was used. All

solvents and reagents were purified and dried by standard techniques.

(a) 5,8-Dimethoxy-1,4-dihydronaphthalene (7)

To a stirred and cooled (-33°) solution of 1,4-dimethoxynaphthalene (6, 0.53 g, 2.8 mmol) in liquid ammonia (20 ml) was added potassium metal (0.672 g, 6 gram atom eq.) in portions during 10 min. After stirring for 30 min at 33° , the colour of the reaction mixture changed from blue to brown. Stirring was continued for further 3 hr at room temperature when most of the ammonia was evaporated. The reaction was quenched by adding absolute ethanol (25 ml) dropwise and stirred for 30 min. Ethanol was removed *in vacuo*, water (25 ml) added and extracted with chloroform. Evaporation of chloroform gave a gummy residue, which on chromatography over silica gel (benzene - hexane, 1:9) afforded pure 7 (0.213 g, 40%) as colourless needles, m.p. 53° (lit.¹² m.p. 50°); PMR (CCl_4): 3.20 (d, 4H, benzylic $-\text{CH}_2$), 3.73 (s, 6H, $2 \times \text{OCH}_3$), 5.80 (t, 2H, vinylic CH), 6.47 (s, 2H, aromatic); M^+ 190 (Found: C, 76.1; H, 7.5. Calc. for $\text{C}_{12}\text{H}_{14}\text{O}_2$: C, 75.8; H, 7.4%). Alternatively 7 was prepared in 90% from *p*-benzoquinone-butadiene adduct (13) as follows:

(b) To a solution of *p*-benzoquinone (54 g, 0.5 mol) in gl. acetic acid (500 ml) was introduced liquid butadiene (81 g, 1.5 mol) at 0° , the reaction mixture allowed to stand at room temperature for 36 hr, and poured over crushed ice with stirring. The colourless compound that precipitated was filtered and dried to obtain 13 (73 g, 90%).

A mixture of 13 (64.8 g, 0.4 mol), dimethyl sulphate (126 g, 1 mol) and potassium carbonate (200 g, 1.4 mol) in dry acetone (1 litre) was refluxed for 48 hr. Usual work-up afforded a solid which was crystallised from methanol to give 7 (68.3 g, 90%) as colourless needles, m.p. 51° (lit.¹² m.p. 50°).

5,8-Dimethoxy-3,4-dihydronaphthalene (9)

To a solution of 7 (0.57 g, 0.003 mol) in dry dimethyl sulphoxide (2.5 ml) was added potassium *t*-butoxide (40 mg, 0.00036 mol) and stirred under nitrogen at room temperature for 6 hr. The reaction mixture was poured over crushed ice and the solid separated was filtered, and crystallised from hexane to give 9 (0.56 g, 98%) as colourless plates, m.p. 70° , PMR (CCl_4): 2.2-2.7 (m, 4H, Hs on C-3 and C-4), 3.73 (s, 6H, $2 \times -\text{OCH}_3$), 5.93, 6.83 (m, 1H each, Hs on C-2 and C-1), 6.53 (s, 2H, aromatic); M^+ 190 (Found: C, 75.7; H, 7.4. $\text{C}_{12}\text{H}_{14}\text{O}_2$ requires C, 75.8; H, 7.4%).

2-Acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (10)

To a solution of 9 (0.95 g, 5 mmol) in chloroform (5 ml) was added a reagent (5 ml), prepared by mixing

N,N-diphenylacetamide (2.1 g, 10 mmol) and PO (1.61 g, 16.6 mmol) in chloroform (5 ml). The reaction mixture was refluxed for 4 hr, saturated aq. sodium acetate added and extracted with chloroform. Dry Na_2SO_4 and evaporation of chloroform gave a gummy product, which on chromatography on silica gel (hexane - benzene 9:1), gave 10 (0.094 g, 10%) yellow needles, m.p. 102° (lit.¹⁰ m.p. 104°); PMR (CDCl_3): 2.37 (s, 3H, COCH_3), 2.23-2.83 (m, 4H $\times \text{CH}_2$), 3.76 (s, 3H, OCH_3), 3.83 (s, 3H, $-\text{OCH}_3$), 6.43, 6.66 (dd, $J = 8$ Hz, 2H aromatic), 7.60 (s, 1H, olefinic); M^+ 232 (Found: C, 72.1; H, 6.9. Calc. for $\text{C}_{14}\text{H}_{16}\text{O}_3$: C, 72.4; H, 6.8%).

2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (11)

A solution of 10 (1 g, 0.004 mol) in ethanol (25 ml) and 5% Pd/C (0.1 g) was hydrogenated at 20 psi at room temperature with mechanical shaking for 5 hr. The catalyst was filtered, washed with ethanol (10 ml) and the combined ethanol solution evaporated to dryness. The colourless residue was crystallised from ethanol-pet. ether (2:1) to give 11 (0.9 g, 90%), m.p. 82° (lit.⁷ m.p. $81-82^{\circ}$); PMR (CDCl_3): 2.2 (s, 3H, COCH_3), 2.2-3.2 (m, 7H, $3 \times \text{CH}_2$ & CH), 3.73 (s, 6H $\times \text{OCH}_3$), 6.46 (s, 2H, Ar-H); M^+ 234 (Found: C, 71.8; H, 7.7. Calc. for $\text{C}_{14}\text{H}_{18}\text{O}_3$: C, 71.8; H, 7.7%).

($\pm$)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (4)

A solution of 11 (0.57 g, 2.45 mmol) in dry *t*-butanol (5 ml) was added to an oxygen saturated solution of potassium *t*-butoxide in *t*-butanol (45 ml). Dry oxygen was bubbled into the solution for 5 min while keeping the reaction at 35° . The solution was cooled to 0° and glacial acetic acid added until it became acidic. Zinc dust (2 g) was immediately added and the solution stirred at room temperature for 6 hr. Zinc dust was filtered off and the filtrate concentrated on a rotary evaporator to give a residue which was diluted with water and extracted with chloroform. The chloroform layer was dried (Na_2SO_4), evaporated and the residue crystallised from methanol-ether to give 4 (0.6 g, 60%) as colourless needles, m.p. 99° (lit.⁸ m.p. 97°); PMR (CDCl_3): 1.85 (t, 2H, C-3H), 2.3 (s, 3H, $-\text{COCH}_3$), 2.76 (t, 2H, Ar- CH_2), 2.8 (bs, 2H, $-\text{CH}_2$), 3.4 (bs, 1H, $-\text{OH}$, D_2O exchangeable), 3.73 (s, 3H, $-\text{OCH}_3$), 3.73 (s, 3H, $-\text{OCH}_3$), 6.6 (s, 2H, H); IR (CHCl_3) 3200 (OH), 1685 cm^{-1} ($\text{C}=\text{O}$); M^+ 250 (Found: C, 67.0; H, 7.2. Calc. for $\text{C}_{14}\text{H}_{18}\text{O}_4$: C, 67.2; H, 7.2%).

5,8-Dimethoxy-3,4-dihydro-2-naphthaldehyde (12)

To a precooled (0°) solution of 9 (38 g, 0.2 mol) in dimethylformamide (80 ml) was added Vilsmeier

Haack reagent and DMF (3 ml) was heated at 80° for 1 hr. The reaction mixture was washed with methanol to give 12 (m.p. $91-92^{\circ}$); PMR (CDCl_3): 2.37 (s, 3H, COCH_3), 2.23-2.83 (m, 4H $\times \text{CH}_2$), 3.76 (s, 3H, OCH_3), 3.83 (s, 3H, $-\text{OCH}_3$), 6.43, 6.66 (dd, $J = 8$ Hz, 2H aromatic), 7.60 (s, 1H, olefinic); M^+ 232 (Found: C, 72.1; H, 6.9. Calc. for $\text{C}_{14}\text{H}_{16}\text{O}_3$: C, 72.4; H, 6.8%).

2-(1-Hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-yl)ethanol (13) was prepared by adding 2.1 mol of 10 to 600 ml of nitroethane for 1 hr. The reaction mixture was added to organic layer (Na_2SO_4) and the combined organic layer was washed with water, dried, and the combined ethanol solution evaporated to dryness. The colourless residue was crystallised from ethanol-pet. ether (2:1) to give 13 (0.9 g, 90%), m.p. 82° (lit.⁷ m.p. $81-82^{\circ}$); PMR (CDCl_3): 2.2 (s, 3H, COCH_3), 2.2-3.2 (m, 7H, $3 \times \text{CH}_2$ & CH), 3.73 (s, 6H $\times \text{OCH}_3$), 6.46 (s, 2H, Ar-H); M^+ 234 (Found: C, 71.8; H, 7.7. Calc. for $\text{C}_{14}\text{H}_{18}\text{O}_3$: C, 71.8; H, 7.7%).

Haack reagent prepared from POCl_3 (46 g, 0.3 mol) and DMF (36.5 g, 0.5 mol). The reaction mixture was heated at 80° for 3 hr and the hot solution poured over crushed ice. The solid that separated was filtered, washed with water, and dried and crystallised from methanol to give 12 (39 g, 90%) as light yellow plates, m.p. $91-92^\circ$ (lit.⁹ m.p. $91-92^\circ$); PMR (CCl_4): 2.03-2.90 (m, 4H, Hs on C-3 and C-4), 3.7 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 6.5 (dd, $J = 8$ Hz, 2H, Ar-H), 7.33 (t, 1H, vinylic H), 9.36 (s, 1H, aldehydic); M^+ 218 (Found: C, 71.6; H, 6.6. Calc. for $\text{C}_{13}\text{H}_{14}\text{O}_3$: C, 71.6; H, 6.4%).

2-(1-Hydroxyethyl)-5,8-dimethoxy-3,4-dihydronaphthalene (14)

To a solution of methylmagnesium iodide (60 ml, 35 g, 2.1 mol) in ether, a solution of 12 (21.8 g, 0.1 mol) in ether (600 ml) was added through a syringe under nitrogen at 10° and then stirred at room temperature for 1 hr. Saturated aluminium chloride solution (100 ml) was added and the mixture stirred for 20 min. The organic layer was separated, washed with water, dried (Na_2SO_4) and concentrated to give (±)-14 as a semisolid, which crystallised from, pet ether in colourless needles. (21.1 g, 90%), m.p. $78-79^\circ$ (lit.⁹ m.p. $78-79^\circ$); PMR (CDCl_3): 1.3 (d, $J = 6$ Hz, 3H, CH_3 -CHOH) 1.73 (bs, 1H, -OH, D_2O exchangeable), 2.06-2.36 (m, 2H, Hs on C-3), 2.56-2.86 (m, 2H, benzylic CH_2), 3.7 (s, 6H, $2 \times -\text{OCH}_3$), 4.1-4.5 (q, $J = 6$ Hz, 1H, - CH_3 -CH-OH), 6.43 (s, 2H, Ar-H), 6.53 (bs, 1H, vinylic H); M^+ 234 (Found: C, 71.9; H, 7.8. Calc. for $\text{C}_{14}\text{H}_{18}\text{O}_3$: C, 71.8; H, 7.7%).

2-Hydroxyethyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (16)

To a solution of 14 (4.68 g, 0.02 mol) in benzene (100 ml) was added vanadyl acetylacetonate (0.1 g, 0.003 mol) followed by *t*-butyl hydroperoxide (70%) (6 ml, 0.045 mol) at room temperature, and stirred for 4 hr. Benzene solution was washed with water and dried (Na_2SO_4). Removal of solvent on rotavapour gave 15 as a thick light brown gummy material which was subjected to LAH reduction as such.

To a solution of 15 in dry tetrahydrofuran (100 ml), LAH (1.14 g, 0.03 mol) was added in portions during 20 min and stirred for 3 hr. Saturated sodium carbonate solution was added at 0° and the contents were stirred for 30 min. The solid separated was filtered and washed with chloroform. The filtrate on evaporation of solvent gave a semisolid which was crystallised from benzene to give colourless needles of (±)-16 (3.53 g, 70%), m.p. 145° (lit.¹⁰ m.p. $145-146^\circ$); PMR (CDCl_3): 1.25 (d, $J = 6$ Hz, 3H, CH_3 -CHOH), 1.5-2.12 (m, 4H, 2H on C-3 and $2 \times \text{OH}$, after D_2O exchange integration reduced to half), 2.44-2.93 (m, 4H, Hs on C-1 and C-4), 3.75 (q, 1H merged with

methoxy groups, CH_3 -CH-OH), 3.75 (s, 3H, - OCH_3), 3.76 (s, 3H, OCH_3), 6.56 (s, 2H, Ar-H).

(±)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (4)

To the Fetizone reagent (20 g) (silver carbonate on celite powder) was added dry benzene (250 ml) and 16 (3 g, 0.012 mol). The contents were refluxed for 2 hr, filtered hot, benzene solution concentrated and passed over a column of silica gel with benzene as eluent to afford (±)-4, (1.8 g, 60%), m.p. 99° (lit.^{8a} 97° ; lit.¹⁰ $100-101^\circ$).

(±)-4-Demethoxy-7-deoxydaunomycinone (5)

An intimate mixture of 4 (0.25 g, 0.001 mol), phthalic anhydride (0.25 g, 0.0016 mol), aluminium chloride (2.5 g) and sodium chloride (0.5 g) was heated at 180° for 5 min. The resultant reddish mass was treated with a saturated solution of oxalic acid to give a red coloured solid, which was filtered, washed with water, dried and chromatographed on a silica gel column using 2% acetone in benzene as eluent to give (±)-5 (0.245 g, 70%) as reddish plates, m.p. $212-15^\circ$ (lit.¹³ m.p. $210-12^\circ$); PMR (CDCl_3): 1.96 (t, 2H, Hs on C-8), 2.36 (s, 3H, COCH_3), 3.03 (m, 4H, Hs on C-7 and C-10), 3.62 (s, 1H, OH, D_2O exchangeable), 7.78 (m, 2H, Ar-H), 8.26 (m, 2H, Ar-H), 13.27 (s, 2H, phenolic OH) (Found: C, 68.3; H, 4.7. Calc. for $\text{C}_{20}\text{H}_{16}\text{O}_6$: C, 68.2, H, 4.6%).

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INDIAN J. CHEM., VOL. 24B, JULY 1985

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