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NOVEL RESOLUTION OF THE ANTHRACYCLINONE INTERMEDIATE BY THE USE OF (2R, 3R)-(+)- and (2S, 3S)-(−)-1,4-BIS(4-CHLOROBENZYLOXY)BUTANE-2,3-DIOL

A SIMPLE AND EFFICIENT SYNTHESIS OF OPTICALLY PURE 4-DEMETHOXYDAUNOMYCINONE AND 4-DEMETHOXYADRIAMYCINONE[1]

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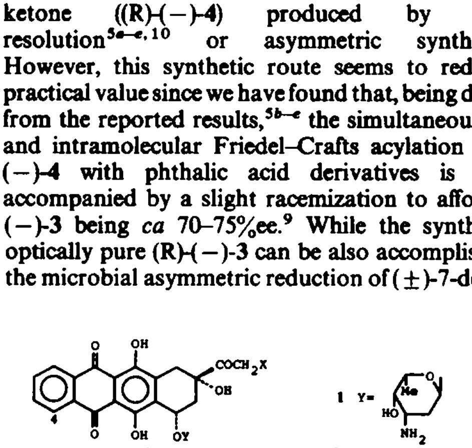
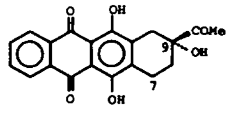
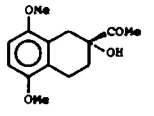
Abstract—(±)-7-Deoxy-4-demethoxydaunomycinone((±)-3) was found to be cleanly resolved by forming a mixture of the diastereomeric acetals ((−)-9 and (+)-10 or (+)-9 and (−)-10) with the title *vicinal*-diol((+)- or (−)-5), affording optically pure (R)-(−)-3. The resolving agents ((+)- and (−)-5) were readily synthesized from unnatural (2S, 3S)-(−)-tartaric acid ((−)-6) or D-(−)-mannitol and natural (2R, 3R)-(+)-tartaric acid ((+)-6), respectively. The undesired enantiomer ((S)-(+)-3) obtained by the optical resolution could be racemized by heating with trifluoromethanesulfonic acid in aq acetic acid. Optically pure (R)-(−)-3 was elaborated to optically pure (+)-4-demethoxydaunomycinone ((+)-2b) and (+)-4-demethoxyadriamycinone ((+)-2a) by featuring highly stereoselective (>20:1) introduction of the OH group into the C_7-position as a key step.

The 4-demethoxyanthracyclines, 4-demethoxyadriamycin (**1a**) and 4-demethoxydaunorubicin (**1b**), attract much attention since improved therapeutic indexes can be expected for these modified antibiotics.[3–5] Although numerous synthetic efforts on anthracyclinones, the aglycones of anthracycline antibiotics, have been devoted to the synthesis of 4-demethoxyadriamycinone (**2a**) and 4-demethoxydaunomycinone (**2b**),[5,6] only a limited number of methods is still available for producing optically active **2a**, **2b**.[5a–e,6b,7–10]

Optically pure (R)-(−)-7-deoxy-4-demethoxydaunomycinone ((R)-(−)-3), from which optically active **2a**, **2b** can be elaborated, is anticipated to hold a pivotal position in the synthesis of optically active **2a**, **2b**.[5,6,9] The tetracyclic α-hydroxy ketone ((R)-(−)-3) can be synthesized from the optically pure bicyclic α-hydroxy ketone ((R)-(−)-4) produced by optical resolution[5a–e,10] or asymmetric synthesis.[7–9] However, this synthetic route seems to reduce its practical value since we have found that, being different from the reported results,[5b–e] the simultaneous inter- and intramolecular Friedel–Crafts acylation of (R)-(−)-4 with phthalic acid derivatives is always accompanied by a slight racemization to afford (R)-(−)-3 being *ca* 70–75%ee.[9] While the synthesis of optically pure (R)-(−)-3 can be also accomplished by the microbial asymmetric reduction of (±)-7-deoxy-4-demethoxydaunomycinone dimethyl ether followed by oxidation and demethylation,[10] this resolution method has been found to be less practical because of the low solubility of the reduction substrate in an aqueous medium and inefficient separation of the two diastereomeric *vicinal*-diols.[10] Recently, along with increased clinical importance of **1a**, **1b**, methods which feature direct optical resolution of (±)-3 with optically active N-aminopyrrolidine derivatives[11] and kinetic resolution by the use of asymmetric epoxidation,[12] have been explored for producing optically pure (R)-(−)-3. Novel syntheses of optically pure **2b** have also been achieved by an asymmetric Diels–Alder reaction[13] and optical resolution of the racemic α-hydroxy acid[14] as key synthetic steps.




(R)-(−)-3


(R)-(−)-4

Considering the usefulness of (R)-(−)-3 in the synthesis of optically pure **2a**, **2b**,[5] another resolution method was sought which can readily afford optically pure (R)-(−)-3 from the corresponding racemic α-hydroxy ketone ((±)-3). We have now found that optically pure (R)-(−)-3 can be prepared by the optical resolution of (±)-3 with a C_2-symmetric *vicinal*-diol.

This report concerns with (1) the efficient optical resolution of (±)-3 in which the C_2-symmetric *vicinal*-diol, (2R, 3R)-(+)- or (2S, 3S) - (−) - 1,4 - bis(4 - chlorobenzyloxy)butane - 2,3 - diol ((+)- or (−)-5), is used as an excellent resolving agent, (2) successful racemization of the partially optically active undesired (S)-(+)-3, which enhances the practical value of the explored resolution method, and (3) further elaboration of (R)-(−)-3 to optically pure **2a**, **2b** by employing a highly stereoselective introduction of the C_7-hydroxyl function.

RESULTS AND DISCUSSION

Reaction of racemic ketone with a C_2-symmetric *vicinal*-diol affords a mixture of the two diastereomeric acetals because the carbon atom of the ketonic function does not become an asymmetric center. While formation of diastereomeric acetals has been occasionally employed for resolving racemic ketones,[15] this resolution method has never met success in the large scale preparation of optically pure ketones since separation of the diastereomeric acetals can usually be accomplished only by gas chromatography.

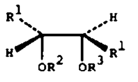
With an aim to finding a suitable C_2-symmetric *vicinal*-diol for resolving (±)-**3**, acetal formations of (±)-**3** were examined by using readily available diols such as (2R, 3R)-(+)-dimethyl tartrate,[16] (2R, 3R)-(−)-butane-2,3-diol,[16] and (2S,3S)-(−)-1,4-bis(benzyloxy)butane-2,3-diol.[17] However, acetal formation was not observed when (2R, 3R)-(+)-dimethyl tartrate was employed as a resolving agent. While both (2R, 3R)-(−)-butane-2,3-diol and (2S, 3S)-(−)-1,4-bis(benzyloxy)butane-2,3-diol gave mixtures of the corresponding diastereomeric acetals in quantitative yields, attempted separations of the acetal mixtures by column chromatography or by recrystallization turned out to be fruitless. After these unsuccessful examinations, (+)- and (−)-**5** were selected as the most suitable C_2-symmetric *vicinal*-diols for optical resolution of (±)-**3** due to the excellent crystallization and separation properties of the diastereomeric acetals. These *vicinal*-diols ((+)- and (−)-**5**) were readily synthesized from unnatural (2S, 3S)-(−)- and natural (2R, 3R)-(+)-tartaric acid ((−)- and (+)-**6**).

p-Chlorobenzylation of (−)-1,4-diol ((−)-**7**), $[\alpha]_D^{20}$ −4.3° ($CHCl_3$), prepared from (−)-**6** according to the reported method,[19,20] followed by acidic hydrolysis of the formed (+)-acetal ((+)-**8**), gave (+)-**5**, $[\alpha]_D^{20}$ +6.4° ($CHCl_3$). Levo-rotatory *vicinal*-diol ((−)-**5**), $[\alpha]_D^{20}$ −6.4° ($CHCl_3$), was similarly prepared from (+)-**6** by way of (+)-**7**, $[\alpha]_D^{20}$ +4.5° ($CHCl_3$), and (−)-**8**. While unnatural (−)-**6** is fairly expensive for a large scale preparation, synthesis of (−)-**7** could be also achieved by using D-(−)-mannitol as the starting material according to the reported procedure with a little modification.[21,22] Thus, triacetal formation of D-(−)-mannitol, followed by partial deacetallization, oxidative cleavage of the two terminal 1,2-diols, and reduction of the dialdehyde, successfully gave (−)-**7**, $[\alpha]_D^{20}$ −4.2° ($CHCl_3$).

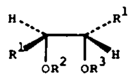
Acetallization of (±)-**3** with (+)-**5** in the presence of p-toluenesulfonic acid gave an oily mixture of the diastereomeric acetals ((−)-**9** and (+)-**10**), $[\alpha]_D^{20}$ +4.8° ($CHCl_3$), in a quantitative yield. The mixture was triturated in ether to give crude (−)-**9** in 47% yield. The ratio of (−)-**9** to (+)-**10** involved in this sample was estimated as 85:15 by the optical purity of (R)-(−)-**3** derived from this sample. Concentration of the mother liquor *in vacuo* afforded crude (+)-**10** in 49% yield. The ratio of (−)-**9** to (+)-**10** present in this sample was similarly calculated as 20:80. Rough separation of (−)-**9** and (+)-**10** could also be accomplished by direct recrystallization of the acetal mixture from ether-dichloromethane. Recrystallization of crude (−)-**9** from acetonitrile gave pure (−)-**9**, $[\alpha]_D^{20}$ −53.6° ($CHCl_3$), in 35% (70% based on (R)-(−)-**3** involved in (±)-**3**) yield. Pure (+)-**10**, $[\alpha]_D^{20}$ +66.8° ($CHCl_3$), could be obtained from crude (+)-**10** in 18% (36% based on (S)-(+)-**3** involved in (±)-**3**) yield by recrystallization from ether. The same acetallization of (±)-**3** with (−)-**5** as that described above, gave a mixture of (+)-**9** and (−)-**10**, $[\alpha]_D^{20}$ −5.4° ($CHCl_3$), in a quantitative yield, from which pure (+)-**9**, $[\alpha]_D^{20}$ +53.8° ($CHCl_3$), and (−)-**10**, $[\alpha]_D^{20}$ −66.4° ($CHCl_3$), could be obtained in 33% and 16% (66% and 32% based on (S)-(+)- and (R)-(−)-**3** involved in (±)-**3**) yields, respectively, by trituration with ether and sequential recrystallizations.

Regeneration of optically pure (R)-(−)-**3** from (−)-**9** was readily accomplished by treating (−)-**9** under the condition for transacetallization catalyzed by boron trifluoride or hydrolysis with aqueous hydrochloric acid, giving optically pure (R)-(−)-**3**, $[\alpha]_D^{20}$ −90.3° ($CHCl_3$), in 98% or 97% yield. When (+)-**10** was similarly subjected to transacetallization, optically pure (S)-(+)-**3**, $[\alpha]_D^{20}$ +89.5° ($CHCl_3$), could be obtained in 97% yield. In completely the same manner, (+)-**9** and (−)-**10** regenerated (S)-(+)- and (R)-(−)-**3**, respectively. Recovery of the resolving agents ((+)- and (−)-**5**) could be simply accomplished since (+)-**8** and (+)-**5** could be readily separated from (R)-(−)-**3** by a short silica gel column (Experimental).

Next, in order to improve efficacy of the explored optical resolution, racemization of the undesired enantiomer ((S)-(+)-**3**) was examined. Attempted racemization of partially optically active (S)-(+)-**3**, 61%ee, derived from crude (+)-**10**, under the same condition as that previously explored for (S)-(+)-**4**,[10] was less effective and proceeded with 30% loss of optical integrity. However, the use of trifluoromethanesulfonic acid in place of p-toluenesulfonic acid was found to give the improved result. Thus, treatment of partially optically active (S)-(+)-**3**, 58%ee, with trifluoromethanesulfonic acid (70 eq) in aqueous acetic acid afford (S)-(+)-**3**, 22%ee, in 62% racemization. Detailed mechanistic studies performed using (S)-(+)-**4** and its



(+)-**5** (−)-**7**
(−)-**6** (+)-**8**



(−)-**5** (+)-**7**
(+)-**6** (−)-**8**

5 $R^1=CH_2OCH_2C_6H_4Cl$-*p*, $R^2=R^3=H$
6 $R^1=COOH$, $R^2=R^3=H$
7 $R^1=CH_2OH$, $R^2=R^3=CMe_2$
8 $R^1=CH_2OCH_2C_6H_4Cl$-*p*, $R^2=R^3=CMe_2$

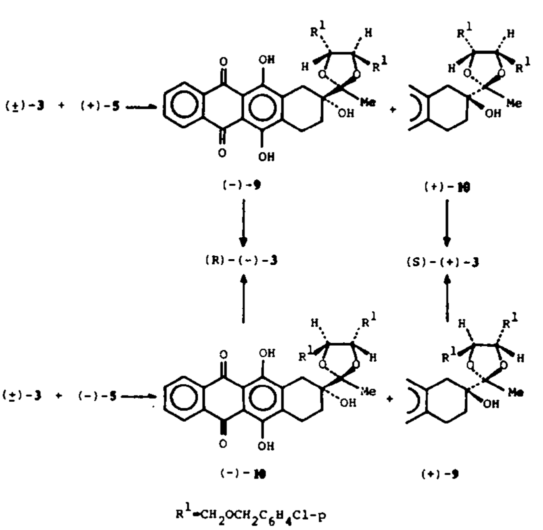


Chart 1.

related compounds,[23] suggest that the racemization probably occurs by way of the ring-expanded 7-membered α-hydroxy ketones.

Since the preparation of optically pure (R)-(−)-**3** was completed, conversion of (R)-(−)-**3** to (+)-**2a**, **2b** was next attempted.

Fairly confused results have been delineated as to the stereoselective introduction of the OH group into the C_7-position of anthracyclinone nuclei.[24] However, it has been generally observed that the solvolytic displacement of 7-bromo-7-deoxy-anthracyclinones results in predominant formation of the $C_{7\beta}$-hydroxy or -acyloxy compounds when the C_9-carbon carries a β-acetyl group,[5b,25,26] whereas the 7α-hydroxy compounds are formed when 7-bromo-7-deoxyanthracyclinones lacking ketonic functions at the $C_{9\beta}$-position were treated with aqueous solvolytic condition.[27–30] Considering these trends, (R)-(−)-acetal ((R)-(−)-**11**), $[\alpha]_D^{20}$ −81.2° ($CHCl_3$), prepared from (R)-(−)-**3** in 98% yield, was first treated with bromine in a two-layered mixture of chloroform-carbon tetrachloride-water under irradiation with a tungsten lamp, to produce an epimeric mixture of 7-bromo-7-deoxy-4-demethoxydaunomycinone. This was immediately treated with 10% aqueous sodium hydroxide solution, then with aqueous hydrochloric acid to hydrolyze the acetal, giving crude (+)-**2b** in 48% yield.[31] Chromatographic (TLC) analysis of the crude sample clearly showed that the ratio of (+)-**2b** to its C_7-epimer was more than 20 : 1. Direct recrystallization of this sample readily afforded optically pure (+)-**2b**, $[\alpha]_D^{20}$ + 156° (dioxane), in 34% yield based on (R)-(−)-**11**. As shown in *Chart 2*, highly stereoselective formation of (+)-**2b** can be explained by the attack of the hydroxide anion H-bonded with the $C_{9\alpha}$-hydroxyl group. The same explanation has been proposed for the stereoselective formation of $C_{9\beta}$-ethyl-$C_{7\alpha}$-hydroxy-anthracyclinones from their 7-deoxy precursors.[28,29]

On the other hand, successive bromination of (R)-(−)-**11** and treatment with aqueous trifluoroacetic acid in the same manner as that reported,[5b] was found to afford a mixture of (+)-**2b** and its C_7-epimer (*ca* 5 : 1) after extractive isolation. Separation of the mixture by column chromatography gave pure (+)-**2b** in 41% yield, which was used as an authentic sample after recrystallization, $[\alpha]_D^{20}$ + 157° (dioxane) (Experimental).

Bromination of (+)-**2b** with pyridinium hydrobromide perbromide according to the reported method,[9b] followed by substitution with potassium acetate and hydrolysis with aqueous sodium carbonate, gave crude (+)-**2a**. Direct recrystallization of this sample from methanol readily afforded optically pure (+)-**2a**, $[\alpha]_D^{20}$ + 170° (dioxane), in 58% yield based on (+)-**2b**.

Due to operational simplicity, use of the readily accessible resolving agent, and racemization of the undesired enantiomer ((S)-(+)-**3**), the optical resolution of (±)-**3** described above is considered to be quite practical. Moreover, functionalization of the C_7-position of (R)-(−)-**3** by way of (R)-(−)-**11** could be accomplished in a highly stereoselective manner, resulting in the isolation of optically pure (+)-**2b** from the reaction mixture by simple recrystallization. Taking into account these novel aspects, the overall process from (±)-**3** to (+)-**2a**, **2b** in which all reaction products can be purified simply by recrystallization, is anticipated to be one of the best procedures for the industrial synthesis of optically pure (+)-**2a**, **2b**.

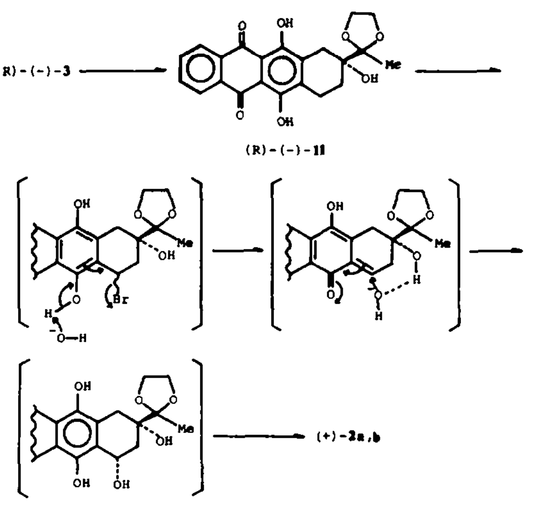


Chart 2.

EXPERIMENTAL[32]

(4R, 5R)-(−)-4,5-*Bis(hydroxymethyl)-2,2-dimethyl*-1,3-*dioxolane*((−)-**7**)

(*a*) *Preparation from* (−)-**6**: Esterification of (−)-**6** (m.p. 169–171°, $[\alpha]_D^{20}$ −12.3° (*c* = 20.0, H_2O)) with EtOH in the presence of conc H_2SO_4 (82%), followed by acetallization with 2,2-dimethoxypropane by the use of *p*-TsOH—H_2O[19] and reduction with lithium aluminium hydride[20] (74% (2 steps)), gave (−)-**7** *via* (2S, 3S)-(−)-diethyl tartrate (b.p. 129–130° (8 mmHg), $[\alpha]_D^{20}$ −9.1° (*c* = 1.04, EtOH)) and (2S, 3S)-(+)-diethyl-2,3 - O - isopropylidene - tartrate (b.p. 114–115° (8 mmHg)). The (−)-dioxolane ((−)-**7**) showed b.p. 100–105° (0.1 mmHg) and $[\alpha]_D^{20}$ −4.3° (*c* = 5.26, $CHCl_3$) (lit.,[22] b.p. 110° (0.25 mmHg), $[\alpha]_D^{19}$ − 1.6° (*c* = 0.32, $CHCl_3$); lit.,[33] b.p. 91–93° (0.01–0.02 mmHg), $[\alpha]_D^{20}$ − 3.1° (*c* = 5.20, $CHCl_3$)).

(*b*) *Preparation from* D-(−)-*mannitol*: Acetallization of D-(−)-mannitol (m.p. 167–170°, $[\alpha]_D^{20}$ −0.3° (*c* = 10.1, H_2O) with Me_2CO and conc H_2SO_4[21] (71%), followed by selective hydrolysis with aq AcOH[33,34] (80%), glycol cleavage with $NaIO_4$[22] and reduction with sodium borohydride (89% (2 steps)) gave (−)-**7** *via* (+)-1,2-3,4-5,6-tris-O-isopropylidene-D-mannitol, m.p. 68–70°, $[\alpha]_D^{20}$ + 13.1° (*c* = 7.80, EtOH), and (+)-3,4-O-isopropylidene-D-mannitol, m.p. 84–86°, $[\alpha]_D^{20}$ +25.3° (*c* = 2.92, EtOH). This diol ((−)-**7**) showed b.p. 105–110° (0.1 mmHg) and $[\alpha]_D^{20}$ −4.2° (*c* = 5.31, $CHCl_3$), and was identified with the authentic sample obtained in (a) by spectral (IR and NMR) comparisons.

(4S,5S)-(+)-4,5-*Bis(hydroxymethyl)-2,2-dimethyl*-1,3-*dioxolane* ((+)-**7**)

This was prepared from (+)-**6** (m.p. 169–171°, $[\alpha]_D^{20}$ + 12.1° (*c* = 21.1, H_2O)) by way of (2R, 3R)-(+)-diethyl tartrate (b.p. 136–139°, $[\alpha]_D^{20}$ + 8.8° (*c* = 2.46, EtOH)) and (2R,3R)-(−)-diethyl 2,3-O-isopropylidenetartrate (b.p. 120–122° (10 mmHg)) according to the same procedure as that described for (−)-**7**. The 1,3-dioxolane ((+)-**7**) obtained showed b.p. 100–105° (0.1 mmHg) and $[\alpha]_D^{20}$ + 4.5° (*c* = 5.06, $CHCl_3$) (lit.,[20] b.p. 96–96.5° (0.5 mmHg), $[\alpha]_D^{20}$ + 4.1° (*c* = 5, $CHCl_3$); lit.,[15b] b.p. 103–104° (0.2 mmHg), $[\alpha]_D^{22}$ + 4.1° (*c* = 5, $CHCl_3$)). This sample showed the same spectral (IR and NMR) properties as those of (−)-**7**.

(4R, 5R)-(+)-4,5-*Bis(4-chlorobenzyloxymethyl)-2,2-dimethyl*-1,3-*dioxolane* ((+)-**8**)

A soln of (−)-**7** ($[\alpha]_D^{20}$ −4.3° (*c* = 5.26, $CHCl_3$)) (3.0 g, 18 mmol) in THF (6 ml) was added to a stirred suspension of sodium hydride (50% oil dispersion) (1.96 g, 41 mmol) in THF (20 ml) below 5° over 15 min, and the mixture was stirred at room temp for 30 min. A soln of *p*-chlorobenzyl chloride (8.94 g, 56 mmol) in THF (15 ml) was added to the mixture at room temp over 15 min, and the stirring was continued at 50° for 3 hr. After cooling, the mixture was diluted with C_6H_6 and H_2O, and the upper organic layer was separated. The aqueous phase was further extracted with C_6H_6, and the combined organic extracts were washed successively with H_2O, 5% HCl, H_2O, satd. $NaHCO_3$, and H_2O. Filtration and concentration *in vacuo*, followed by purification by column chromatography (SiO_2, C_6H_6), afforded pure (+)-**8** (6.54 g, 86%), $[\alpha]_D^{20} + 8.1°$ ($c = 6.17$, $CHCl_3$). IRν_{max}^{film}cm^{-1}: 1600, 1495, 1090. NMR (in $CDCl_3$): 1.41 (6H, two s, $C\underline{H}_3 \times 2$), 3.5–3.7 (4H, m, $CHC\underline{H}_2O \times 2$), 3.9–4.1 (2H, m, $C\underline{H}CH_2 \times 2$), 4.50 (4H, s, $OC\underline{H}_2Ar \times 2$), 7.05–7.35 (8H, m, aromatic protons). Mass: *m/e*: 410 (M^+).

(4S, 5S)-(−)-4,5-*Bis*(4-*chlorobenzyloxymethyl*)-2,2-*dimethyl*-1,3-*dioxolane* ((−)-**8**)

The same treatments of (+)-**7** ($[\alpha]_D^{20} + 4.5°$ ($c = 5.06$, $CHCl_3$)) (1.0 g, 6.2 mmol) as those of (−)-**7** gave (−)-**8** (2.12 g, 84%), $[\alpha]_D^{20} - 8.2°$ ($c = 6.14$, $CHCl_3$), after purification with column chromatography (SiO_2, C_6H_6). Spectral (IR and NMR) properties of this sample were identical with those of (+)-**8**.

(2R, 3R)-(+)-1,4-*Bis*(4-*chlorobenzyloxy*)*butane*-2,3-*diol* ((+)-**5**)

A mixture of (+)-**8** ($[\alpha]_D^{20} + 8.1°$ ($c = 6.17$, $CHCl_3$)) (5.0 g, 12 mmol) and 5% HCl (1 ml) in MeOH (15 ml) was heated at reflux for 5 hr. After concentration *in vacuo*, the residue was diluted with Et_2O and satd. $NaHCO_3$, and the upper ethereal layer was separated. The lower aqueous phase was further extracted with Et_2O, and the combined ethereal extracts were washed with satd NaCl. Filtration and concentration *in vacuo* gave pure (+)-**8** (4.2 g, 93%), m.p. 76–77°. Recrystallization from toluene-hexane gave an analytical sample, m.p. 76–77°, $[\alpha]_D^{20} + 6.4°$ ($c = 3.11$, $CHCl_3$). IRν_{max}^{KBr}cm^{-1}: 3250, 1598, 1493, 1085. NMR (in $CDCl_3$): 2.6–2.9 (2H, m, $O\underline{H} \times 2$), 3.4–3.7 (4H, m, $CHC\underline{H}_2O \times 2$), 3.70–4.0 (2H, m, $C\underline{H} \times 2$), 4.47 (4H, s, $C\underline{H}_2Ar \times 2$), 7.05–7.35 (8H, m, aromatic protons). (Found: C, 58.27; H, 5.31. Calc for $C_{18}H_{20}Cl_2O_4$: C, 58.23; H, 5.43%). Mass: *m/e*: 371 ($[M+1]^+$).

(2S, 3S)-(−)-1,4-*Bis*(4-*chlorobenzyloxy*)*butane*-2,3-*diol* ((−)-**5**)

Hydrolysis of (−)-**8** ($[\alpha]_D^{20} - 8.0°$ ($c = 6.01$, $CHCl_3$)) (5.0 g, 12 mmol) in the same manner as that for (+)-**8** gave pure (−)-**5** (4.1 g, 91%), m.p. 74–77°, after extractive isolation and concentration *in vacuo*. Recrystallization from toluene-hexane gave an analytical sample, m.p. 75–77°, $[\alpha]_D^{20} - 6.4°$ ($c = 3.04$, $CHCl_3$). Spectral (IR, NMR, and Mass) properties of this sample were superimposable on those of (+)-**5**. (Found: C, 58.53; H, 5.44. Calc for $C_{18}H_{20}Cl_2O_4$: C, 58.23; H, 5.43%).

(±)-2-*Acetyl*-2,5,12-*trihydroxy*-1,2,3,4-*tetrahydronaphthacene*-6,11-*dione* ((±)-7-*deoxy*-4-*demethoxydaunomycinone*) ((±)-**3**)

Prepared from (±)-**4** according to the reported method.[9,10] Yield 89%, m.p. 215–216.5° (lit.,[9] m.p. 214–216°; lit.,[10] m.p. 214–216°).

(2R, 4′R, 5′R)-(−)-2-4′,5′-*Bis*(4-*chlorobenzyloxymethyl*)-2′-*methyl*-1′,3′-*dioxolan*-2′-*yl*-2,5,12-*trihydroxy*-1,2,3,4-*tetrahydronaphthacene*-6,11-*dione* ((−)-**9**) *and its* (2S, 4′R, 5′R)-(+)-*Isomer* ((+)-**10**)

A mixture of (±)-**3** (2.5 g, 7.1 mmol), (+)-**5** (m.p. 76–77°, $[\alpha]_D^{20} + 6.4°$ ($c = 3.11$, $CHCl_3$)) (3.03 g, 8.1 mmol), and *p*-TsOH-H_2O (81 mg, 0.43 mmol) in C_6H_6 (100 ml) was heated at reflux for 13 hr in a Dean–Stark apparatus to remove the water formed. After being cooled, the mixture was diluted with CH_2Cl_2 (100 ml), and neutralized by adding powdered K_2CO_3 (5 g). Filtration and concentration *in vacuo* gave a red oil which was filtered through a short silica gel column (C_6H_6—CH_2Cl_2 1:1) to remove polar impurities, giving a mixture of (−)-**9** and (+)-**10** as a red foam (5.2 g, quantitative yield), $[\alpha]_D^{20} + 4.8°$ ($c = 0.65$, $CHCl_3$), after concentration *in vacuo*. Et_2O (200 ml) was added to the red foam, and the mixture was stirred at room temperature for 15 hr to give red powderlike crystals enriched with (−)-**9** (2.35 g, 47%), m.p. 132–136°. Since this sample afforded partially optically active (R)-(−)-**3**, m.p. 195–200°, $[\alpha]_D^{20} - 63.1°$ ($c = 0.124$, $CHCl_3$), 70%ee, in 92% yield on acidic hydrolysis, the ratio of (−)-**9** to (+)-**10** could be calculated as 85:15. Two recrystallizations of a part of crude (−)-**9** (1.24 g), m.p. 132–136°, from MeCN gave pure (−)-**9** (0.86 g, 35% (70% based on (R)-(−)-**3**, involved in (±)-**3**), m.p. 141–142°, $[\alpha]_D^{20} - 53.6°$ ($c = 0.50$, $CHCl_3$). IRν_{max}^{KBr}cm^{-1}: 3580, 3380, 1615, 1585. NMR (in $CDCl_3$): 1.50 (3H, s, $C\underline{H}_3$), 1.6–2.4 (2H, m, $ArCH_2C\underline{H}_2$), 2.74 (1H, s, $O\underline{H}$), 2.8–3.2 (4H, m, $ArC\underline{H}_2 \times 2$), 3.5–3.9 (4H, m, $CHC\underline{H}_2O \times 2$), 4.2–4.4 (2H, m, $C\underline{H} \times 2$), 4.50, 4.53 (4H, two m, $ArC\underline{H}_2O \times 2$), 7.1–7.4 (8H, m, $ClC_6\underline{H}_4 \times 2$), 7.65–7.8 and 8.15–8.4 (4H, two m, $C_6\underline{H}_4(CO)_2$), 13.1–13.3 (2H, m, $ArO\underline{H} \times 2$). (Found: C, 64.42; H, 4.90. Calc for $C_{38}H_{34}Cl_2O_9$: C, 64.69; H, 4.86%).

Mother liquor from the trituration with Et_2O was concentrated *in vacuo* to give a red foam enriched with (+)-**10** (2.47 g, 49%). Since this sample afforded partially optically active (S)-(+)-**3**, m.p. 190–196°, $[\alpha]_D^{20} + 55.5°$ ($c = 0.110$, $CHCl_3$), 62%ee, in 90% yield on acidic hydrolysis, the ratio of (−)-**9** to (+)-**10** could be estimated as 19:81. Three recrystallizations of a part of crude (+)-**10** (1.24 g) from Et_2O gave pure (+)-**10** (0.47 g, 18% (36% based on (S)-(+)-**3** involved in (±)-**3**)), m.p. 120–121°, $[\alpha]_D^{20} + 66.8°$ ($c = 0.51$, $CHCl_3$). IRν_{max}^{KBr}cm^{-1}: 3450, 1618, 1584. NMR (in $CDCl_3$): 1.48 (3H, s, $C\underline{H}_3$), 1.6–2.1 (2H, m, $ArCH_2C\underline{H}_2$), 2.73 (1H, s, $O\underline{H}$), 2.6–3.3 (4H, m, $ArC\underline{H}_2 \times 2$), 3.4–3.9 (4H, m, $CHC\underline{H}_2O \times 2$), 4.1–4.4 (2H, m, $C\underline{H} \times 2$), 4.52 (4H, s, $OC\underline{H}_2Ar \times 2$), 7.0–7.3 (8H, m, $ClC_6\underline{H}_4 \times 2$), 7.6–7.8 and 8.1–8.4 (4H, two s, $C_6\underline{H}_4(CO)_2$), 13.2 (2H, two s, $ArO\underline{H} \times 2$). (Found: C, 64.52; H, 4.83. Calc for $C_{38}H_{34}Cl_2O_9$: C, 64.69; H, 4.86%).

(2S, 4′S, 5′S)-(+)-2-4′,5′-*Bis*(4-*chlorobenzyloxymethyl*)-2′-*methyl*-1′,3′-*dioxolan*-2′-*yl*-2,5,12-*trihydroxy*-1,2,3,4-*tetrahydronaphthacene*-6, 11-*dione* ((+)-**9**) *and its* (2S, 4′S, 5′S)-*isomer* ((−)-**10**)

A mixture of (±)-**3** (500 mg, 1.4 mmol), (−)-**5** (m.p. 75–77°, $[\alpha]_D^{20} - 6.4°$ ($c = 3.04$, $CHCl_3$)) (606 mg, 1.6 mmol), and TsOH—H_2O (16.2 mg, 0.085 mmol) in C_6H_6 (20 ml) was treated in a similar manner to that for the acetallization with (+)-**5**, giving a mixture of (+)-**9** and (−)-**10** as a red foam (1.02 g, quantiative yield), $[\alpha]_D^{20} - 5.4°$ ($c = 0.61$, $CHCl_3$), after purification by a short silica gel column (SiO_2 (20 g), C_6H_6—CH_2Cl_2 1:1). Treatment of this foam with Et_2O (20 ml) gave red powderlike crystals enriched with (+)-**9** (449 mg, 45%), m.p. 133–138°. The ratio of (+)-**9** to (−)-**10** could be estimated as 85:15 since the acidic hydrolysis of this sample gave partially optically active (S)-(+)-**3**, m.p. 195–201°, $[\alpha]_D^{20} + 62.6°$ ($c = 0.098$, $CHCl_3$), 69%ee, in 90% yield. Two recrystallizations of a part of this crystals (108 mg) from MeCN gave pure (+)-**9** as red crystals (59 mg, 33% (66% based on (S)-(+)-**3** involved in (±)-**3**)), m.p. 141–142°, $[\alpha]_D^{20} + 53.8°$ ($c = 0.55$, $CHCl_3$). Spectral (IR and NMR) properties of this sample were identical with those of (−)-**9**. (Found: C, 64.76; H, 4.74. Calc for $C_{38}H_{34}Cl_2O_9$: C, 64.69; H, 4.86%).

Mother liquor from the trituration with Et_2O was concentrated *in vacuo* to afford a red foam enriched with (−)-**10** (500 mg, 50%). Since this sample gave partially optically active (R)-(−)-**3**, m.p. 193–199°, $[\alpha]_D^{20} - 58.5°$ ($c = 0.102$, $CHCl_3$), 65%ee, in 89% yield on acidic hydrolysis, the ratio of (+)-**9** to (−)-**10** could be calculated as 18:82. Three recrystallizations of a part of this foam (286 mg) from Et_2O gave pure (−)-**10** as red crystals (117 mg, 16% (32% based on (R)-(−)-**3** involved in (±)-**3**), m.p. 120–121°, $[\alpha]_D^{20} - 66.4°$ ($c = 0.53$, $CHCl_3$). This sample showed the same spectral (IR and

NMR) properties as those of (+)-**10**. (Found: C, 64.64; H, 4.92. Calc for $C_{38}H_{34}Cl_2O_9$: C, 64.69; H, 4.86%).

(R)-(−)-2-*Acetyl-2,5,12-trihydroxy-1,2,3,4-tetrahydronaphthacene-6,11-dione* ((−)-7-*deoxy-4-demethoxydaunomycinone*) ((R)-(−)-**3**)

(*a*) *Preparation of authentic* (R)-(−)-**3** from (R)-(−)-**4**: Treatment of (R)-(−)-**4** (m.p. 128–129°, $[\alpha]_D^{20} -46.6°$ ($c = 0.78$, $CHCl_3$))[9,10] according to the reported method,[9,10] gave partially optically active (R)-(−)-**3** in 75% yield, m.p. 206–209°C, $[\alpha]_D^{20} -74.1°$ ($c = 0.108$, $CHCl_3$), 82%ee.[9,10] Repeated recrystallizations from C_6H_6 afforded optically pure (R)-(−)-**3** as red crystals, m.p. 218–219.5°, $[\alpha]_D^{20} -90.0°$ ($c = 0.106$, $CHCl_3$) (lit.,[5b] m.p. 228–230°, $[\alpha]_D^{20} -87°$ ($c = 0.1$, $CHCl_3$); lit.,[5e] m.p. 210–212°, $[\alpha]_D^{20} -84°$ ($c = 0.1$, $CHCl_3$); lit.,[9] m.p. 218–220°, $[\alpha]_D^{20} -87.0°$ ($c = 0.115$, $CHCl_3$)). IR ν_{max}^{KBr} cm^{-1}: 3400, 1700, 1618, 1585. NMR (in $CDCl_3$): 1.8–2.2 (2H, m, $ArCH_2C\underline{H}_2$), 2.39 (3H, s, $C\underline{H}_3$), 2.8–3.4 (4H, m, $ArC\underline{H}_2 \times 2$), 3.78 (1H, s, $O\underline{H}$), 7.7–7.9 and 8.2–8.5 (4H, two m, aromatic protons), 13.43 (2H, two s, $ArO\underline{H} \times 2$). These spectral features were identical with those reported.[9b] This sample was used as an authentic sample of (R)-(−)-**3**.

(*b*) *Preparation from* (−)-**9** *by acidic hydrolysis* (*small scale experiment*): A mixture of (−)-**9** (m.p. 141.5–142°, $[\alpha]_D^{20} -53.6°$ ($c = 0.51$, $CHCl_3$)) (100 mg, 0.14 mmol) and conc HCl (1 ml) in a mixture of THF (2 ml) and dioxane (5 ml) was heated at reflux for 2 hr, diluted with satd $NaHCO_3$, then extracted with $CHCl_3$. The combined organic extracts were washed with H_2O, filtered, and concentrated *in vacuo*. Separation of the residue by column chromatography (SiO_2, C_6H_6—CH_2Cl_2 3:1) gave (R)-(−)-**3** (48.2 mg, 97%), $[\alpha]_D^{20} -84.7°$ ($c = 0.118$, $CHCl_3$). Recrystallization from C_6H_6 gave pure (R)-(−)-**3**, m.p. 217–219°C, $[\alpha]_D^{20} -90.3$ ($c = 0.106$, $CHCl_3$). IR and NMR spectra of this sample were identical with those of the authentic sample (see (a)).

The silica gel column was further eluted with the same solvent, giving crude (+)-**5** after concentration of the combined eluates *in vacuo*. Purification of this sample by PTLC (SiO_2, CH_2Cl_2) gave pure (+)-**5** as a solid (39.4 mg, 75%), m.p. 76–78°C, $[\alpha]_D^{20} +5.7°$ ($c = 2.98$, $CHCl_3$). This was identified with authentic (+)-**5** by spectral (IR and NMR) comparisons.

(*c*) *Preparation from* (−)-**9** *by acidic hydrolysis* (*large scale experiment*): A suspension of (−)-**9** (m.p. 141–142°, $[\alpha]_D^{20} -53.4°$ ($c = 0.52$, $CHCl_3$)) (5.0 g, 7.1 mmol) in a mixture of conc HCl (25 ml), EtOH (50 ml), and THF (50 ml) was heated at reflux for 5 hr. After cooling, the mixture was diluted with EtOH (30 ml), and (R)-(−)-**3** was collected by filtration, washed successively with EtOH, satd. $NaHCO_3$, H_2O, EtOH, and Et_2O, then dried *in vacuo*. It weighed 2.25 g (90%), and showed m.p. 217–218° and $[\alpha]_D^{20} -89.4°$ ($c = 0.108$, $CHCl_3$). IR and NMR spectra of this sample were identical with those of authentic (R)-(−)-**3**.

The ethanolic and aqueous washings were combined and concentrated *in vacuo*. The residual aqueous mixture was extracted with Et_2O. The combined ethereal extracts were washed with satd $NaHCO_3$ and satd NaCl, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, CH_2Cl_2) to afford (+)-**5** as a solid (2.15 g, 82%), m.p. 74–76°, $[\alpha]_D^{20} +6.0°$ ($c = 3.01$, $CHCl_3$). Recrystallization from toluene-hexane gave pure (+)-**5** as colorless crystals, m.p. 76–78°, $[\alpha]_D^{20} +6.4°$ ($c = 2.99$, $CHCl_3$). This was also identified with authentic (+)-**5** by spectral (IR and NMR) comparisons.

(*d*) *Preparation from* (−)-**9** *by transacetallization*: A mixture of (−)-**9** m.p. 141.5–142°, $[\alpha]_D^{20} -53.6°$ ($c = 0.51$, $CHCl_3$)) (200 mg, 0.28 mmol) and boron trifluoride-etherate (0.36 ml) in Me_2CO (20 ml) was heated at reflux for 13 hr. After cooling, the mixture was diluted with satd $NaHCO_3$, and extracted with $CHCl_3$. The combined organic extracts were washed with H_2O. Filtration and concentration *in vacuo*, followed by separation with column chromatography (SiO_2, C_6H_6—CH_2Cl_2 3:1), gave (R)-(−)-**3** (97.8 mg, 98%), $[\alpha]_D^{20} -81.9°$ ($c = 0.116$, $CHCl_3$), and crude (+)-**8**.

Recrystallization of (R)-(−)-**3** from C_6H_6 gave a pure sample, m.p. 218–219°, $[\alpha]_D^{20} -89.9°$ ($c = 0.102$, $CHCl_3$). IR and NMR spectra of this sample were identical with those of authentic (R)-(−)-**3**.

Further purification of crude (+)-**8** with PTLC (SiO_2, CH_2Cl_2) gave pure (+)-**8** (81.6 mg, 70%), b.p. 260° (0.01–0.02 mmHg) (bath temp), $[\alpha]_D^{20} +7.8°$ ($c = 5.97$, $CHCl_3$). This sample showed the same spectral (IR and NMR) properties as those of authentic (+)-**8**.

(*e*) *Preparation from* (−)-**10** *by transacetallization*: The same treatment of (−)-**10** (m.p. 120–121°, $[\alpha]_D^{20} -66.3°$ ($c = 0.51$, $CHCl_3$)) (100 mg, 0.14 mmol) as those for (−)-**9** gave (R)-(−)-**3** as a red solid (49.0 mg, 98%), $[\alpha]_D^{20} -84.6°$ ($c = 0.112$, $CHCl_3$). Recrystallization from C_6H_6 gave pure (R)-(−)-**3** as red crystals, m.p. 218–219°, $[\alpha]_D^{20} -90.1°$ ($c = 0.108$, $CHCl_3$). IR and NMR spectra of this sample were superimposable on those of authentic (R)-(−)-**3**.

(S)-(+)-2-*Acetyl-2,5,12-trihydroxy-1,2,3,4-tetrahydronaphthacene-6,11-dione* ((+)-7-*deoxy-4-demethoxydaunomycinone*) ((S)-(+)-**3**)

(*a*) *Preparation from* (+)-**10** *by transacetallization*: Treatment of (+)-**10** (m.p. 120–121°, $[\alpha]_D^{20} +66.8°$ ($c = 0.51$, $CHCl_3$)) (100 mg, 0.14 mmol) under the same condition as for (−)-**9** gave (S)-(+)-**3** (48.4 mg, 97%), $[\alpha]_D^{20} +84.2°$ ($c = 0.106$, $CHCl_3$), after extractive isolation and chromatographic purification. Recrystallization from C_6H_6 gave pure (S)-(+)-**3**, m.p. 218–219°, $[\alpha]_D^{20} +89.5°$ ($c = 0.102$, $CHCl_3$). IR and NMR spectra of this sample were identical with those of authentic (R)-(−)-**3**.

(*b*) *Preparation from* (+)-**9** *by transacetallization*: The same treatment of (+)-**9** (m.p. 141–142°, $[\alpha]_D^{20} +53.4°$ ($c = 0.53$, $CHCl_3$)) (100 mg, 0.14 mmol) as for (−)-**9** gave (S)-(+)-**3** (49.3 mg, 99%), $[\alpha]_D^{20} +83.7°$ ($c = 0.104$, $CHCl_3$). Recrystallization from C_6H_6 gave pure sample, m.p. 218–219.5°, $[\alpha]_D^{20} +89.8°$ ($c = 120$, $CHCl_3$). This was similarly identified by spectral (IR and NMR) comparisons.

Racemization of partially optically active (S)-(+)-2-*acetyl-2,5,12-trihydroxy-1,2,3,4-tetrahydronaphthacene-6,11-dione* ((S)-(+)-**3**)

Partially optically active (S)-(+)-**3** (m.p. 190–196°, $[\alpha]_D^{20} +53.1°$ ($c = 0.100$, $CHCl_3$)) (20 mg, 0.057 mmol), prepared from a mixture of (−)-**9** and (+)-**10** by transacetallization, was dissolved in a mixture of trifluoromethanesulfonic acid (0.35 ml, 4.0 mmol), AcOH (0.68 ml), and H_2O (0.40 ml), and the mixture was heated at 110° for 20 hr in a sealed tube. After cooling, the mixture was poured onto H_2O, and extracted with $CHCl_3$. The combined chloroform extracts were washed with satd $NaHCO_3$, H_2O, and satd NaCl, filtered, then concentrated *in vacuo*. Purification of the residue by column chromatography (SiO_2, CH_2Cl_2) gave partially racemized (S)-(+)-**3** as a red solid (15.4 mg, 77%), $[\alpha]_D^{20} +20.3°$ ($c = 0.118$, $CHCl_3$), 22%ee, 62% racemization.[23]

(R)-(−)-2-2′-*Methyl-1′,3′-dioxolan-2′-yl-2,5,12-trihydroxy-1,2,3,4-tetrahydronaphthacene-6,11-dione* ((R)-(−)-**11**)

A mixture of (R)-(−)-**3** (m.p. 218–219°, $[\alpha]_D^{20} -90.0°$ ($c = 0.102$, $CHCl_3$)) (160 mg, 0.45 mmol), ethylene glycol (0.24 ml, 4.3 mmol), and *p*-TsOH—H_2O (8 mg, 0.042 mmol) in C_6H_6 (16 ml) was heated at reflux for 5 hr using a Dean–Stark apparatus to remove the water formed. After concentration *in vacuo*, the residue was dissolved in CH_2Cl_2 (30 ml). The organic soln was washed successively with satd $NaHCO_3$, H_2O, and satd NaCl. Filtration and concentration *in vacuo* gave (R)-(−)-**11** as a red solid (177 mg, 98%), m.p. 222–225°. Recrystallization from C_6H_6 gave an analytical sample, m.p. 224–226°, $[\alpha]_D^{20} -81.0°$ ($c = 0.120$, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3500, 1620, 1585. NMR (in $CDCl_3$): 1.46 (3H, s, $C\underline{H}_3$), 1.55 (1H, s, $O\underline{H}$), 1.9–2.1 (2H, m, $ArCH_2C\underline{H}_2$), 2.7–3.2 (4H, m, $ArC\underline{H}_2 \times 2$), 4.08 (4H, s, $OC\underline{H}_2C\underline{H}_2O$), 7.6–7.9 and 8.2–8.4 (4H, two m, aromatic protons), 13.50, 13.52 (2H, two s, $ArO\underline{H} \times 2$).

(Found: C, 66.59; H, 5.05. Calc for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09%).

(+)-4-*Demethoxydaunomycinone* ((+)-**2b**)

(*a*) *Preparation of* (+)-**2b** *according to the reported method*:[5b] A soln of Br_2 in CCl_4 (0.05 M) (6 ml, 0.30 mmol) was added to a soln of (R)-(−)-**11** (m.p. 214–216°, $[\alpha]_D^{20} - 81.0°$ ($c = 0.120$, $CHCl_3$)) (90 mg, 0.28 mmol) and azobisisobutyronitrile (AIBN) (20 mg, 0.12 mmol) in a mixture of $CHCl_3$ (15 ml) and H_2O (12 ml), and the two layer mixture was heated at reflux for 2.5 hr. After 1 hr's and 1.5 hrs' reactions, further amounts of a soln of Br_2 in CCl_4 (0.05 M) (1.5 ml × 2, 0.15 mmol, total 0.45 mmol) were repeatedly added to the mixture. After being cooled, the mixture was diluted with $CHCl_3$ (20 ml), then the lower organic phase was separated. The aqueous phase was further extracted with $CHCl_3$, and the combined organic extracts were washed with H_2O, filtered, then concentrated *in vacuo*. The residue, was directly dissolved in aqueous 80% trifluoroacetic acid (9 ml). The acidic soln was stirred at room temp for 15 hr, poured onto an ice-water, and extracted with $CHCl_3$. The chloroform extracts were combined and washed successively with H_2O, aq. $NaHCO_3$, and H_2O. Filtration and concentration *in vacuo* gave a crude mixture of (+)-**2b** and its $C_{7\beta}$-epimer (110 mg). TLC analysis of this sample showed that the ratio of (+)-**2b** to its epimer is *ca* 5:1. Separation by column chromatography (SiO_2, CH_2Cl_2) afforded (+)-**2b** as a red solid (34.2 mg, 41%). Recrystallization from $CHCl_3$—EtO_2 gave pure (+)-**2b** as red crystals, m.p. 184–185.5°, $[\alpha]_D^{20} + 157°$ ($c = 0.114$, dioxane) (lit.,[9b] m.p. 183.5–184.5°, $[\alpha]_D^{20} + 153°$ ($c = 0.09$, dioxane); lit.,[14b] m.p. 182.5–183°, $[\alpha]_D^{20} + 164.5°$ ($c = 0.1$ dioxane); lit.,[5b] m.p. 184–186°, $[\alpha]_D^{20} + 170°$ ($c = 0.1$ dioxane); lit.,[5c] m.p. 185–187°, $[\alpha]_D^{20} + 165°$ ($c = 0.1$, dioxane)). This was used as an authentic sample of (+)-**2b**. IR ν_{max}^{KBr} cm^{-1}: 3350, 1715, 1620, 1585. NMR (in $CDCl_3$): 2.14 (1H, dd, J = 15 and 5 Hz, $\underline{H}_{8a}$), 2.32 (1H, dt, J = 15 and 2 Hz, $\underline{H}_{8e}$), 2.40 (3H, s, $C\underline{H}_3$), 2.91 (1H, d, J = 19 Hz, $\underline{H}_{10a}$), 3.31 (1H, dd, J = 19 and 2 Hz, $\underline{H}_{10e}$), 3.82 (1H, d, J = 6 Hz, $C_{7\alpha}$—$O\underline{H}$), 4.53 (1H, s, C_9—$O\underline{H}$), 5.23 (1H, m, $\underline{H}_7$), 7.6–7.9 and 8.1–8.3 (4H, two m, aromatic protons), 13.01 and 13.29 (2H, two s, $ArO\underline{H} \times 2$). (Found: C, 65.08; H, 4.35. Calc for $C_{20}H_{16}O_7$: C, 65.22; H, 4.38%). Separation of the $C_{7\beta}$-epimer of (+)-**2b** was not attempted.

(*b*) *Preparation of* (+)-**2b** *by the direct treatment of the epimeric bromides under aqueous alkaline condition*: A soln of Br_2 in CCl_4 (0.05 M) (30 ml, 1.5 mmol) was added to the two-layered soln of (R)-(−)-**11** (m.p. 215–216°, $[\alpha]_D^{20} - 81.2°$ ($c = 0.118$, $CHCl_3$)) (1.2 g, 3.0 mmol) in a mixture of $CHCl_3$ (120 ml), CCl_4 (60 ml), and H_2O (90 ml). The mixture was stirred at 50–55° for 15 min under irradiation with a 60W tungsten lamp. Five 10-ml aliquots of a soln of Br_2 in CCl_4 (0.05 M) were added at 5 min intervals to the stirred mixture (total 50 ml, 2.5 mmol). After addition to the Br_2 soln was over, the whole was further stirred at 50–55° under irradiation for 45 min, then cooled to 20°. 10% NaOH (8 ml) was directly added to the cooled mixture, and the alkaline two-layered mixture was vigorously stirred for 15 min, then acidified with 5% HCl (16 ml). The lower organic phase was separated, and the aqueous layer was further extracted with $CHCl_3$. The combined organic extracts were washed successively with satd $NaHCO_3$ and satd NaCl, filtered, and concentrated *in vacuo*. Conc HCl (36 ml) was added to a soln of the residue in THF (60 ml), and the mixture was stirred at room temp for 12 hr. After being cooled in an ice bath, the mixture was poured onto H_2O, and extracted with $CHCl_3$. The combined extracts were washed with satd $NaHCO_3$ and satd NaCl. Filtration and concentration *in vacuo* gave crude (+)-**2b** (0.87 g). TLC analysis of this sample (SiO_2, $CHCl_3$) showed that the ratio of (+)-**2b** to its $C_{7\beta}$-epimer was more than 20:1. Two recrystallizations of this sample from C_6H_6 gave pure (+)-**2b** (0.38 g, 34%), m.p. 184–185°, $[\alpha]_D^{20} + 156°$ ($c = 0.102$, dioxane). IR and NMR spectra of (+)-**2b** were identical with those of the authentic sample prepared in (a). The mother liquors of the repeated recrystallizations were combined, concentrated *in vacuo*, then separated by column chromatography (SiO_2, $CHCl_3$), giving additional (+)-**2b** as a red solid (0.16 g, 14%, total 48%), m.p. 178–182°.

(+)-4-*Demethoxyadriamycinone* ((+)-**2a**)

Pyridinium hydrobromide perbromide (100 mg, 0.31 mmol) was added to a soln of (+)-**2b** (m.p. 184–185°, $[\alpha]_D^{20} + 156°$ ($c = 0.102$, dioxane)) (100 mg, 0.27 mmol) in THF (10 ml). The mixture was stirred at room temp for 2 hr, and was diluted with Me_2CO (10 ml). After stirring for 15 min, anhyd KOAc (250 mg, 2.5 mmol) was added to the mixture. The mixture was stirred at room temp for 1 hr, concentrated *in vacuo*, then diluted with CH_2Cl_2 and H_2O. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O and satd NaCl. Filtration and concentration *in vacuo* gave a red residue which was suspended in MeOH (40 ml). After addition of 5% Na_2CO_3 (4 ml), the methanolic mixture was heated at 60° for 5 min, cooled, then concentrated *in vacuo* at room temp to half volume. The residual mixture was diluted with satd NaCl, and extracted with THF. The organic extracts were combined, washed with satd NaCl, filtered, then concentrated *in vacuo*, giving crude (+)-**2a** as a red solid. Two recrystallizations of this sample from MeOH gave pure (+)-**2a** (60.6 mg, 58%), m.p. 190–192°, $[\alpha]_D^{20} + 170°$ ($c = 0.110$, dioxane) (lit.,[9b] m.p. 174–176°, $[\alpha]_D^{20} + 147°$ ($c = 0.10$, dioxane)). IR ν_{max}^{KBr} cm^{-1}: 3420, 1720, 1620, 1585. NMR (in $CDCl_3$): 2.18 (1H, dd, J = 15 and 5 Hz, $\underline{H}_{8a}$), 2.35 (1H, dt, J = 15 and 2 Hz, $\underline{H}_{8e}$), 2.97 (1H, t, J = 5 Hz, C_{14}—$O\underline{H}$), 3.01 (1H, d, J = 19 Hz, $\underline{H}_{10a}$), 3.29 (1H, dd, J = 19 and 2 Hz, $C\underline{H}_2OH$), 5.38 (1H, m, $\underline{H}_7$), 7.7–8.0 and 8.2–8.5 (4H, two m, aromatic protons), 13.23 and 13.57 (2H, two s, $ArO\underline{H} \times 2$). Found: C, 62.23; H, 4.41. Calc for $C_{20}H_{16}O_8$: C, 62.50; H, 4.20).

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REFERENCES AND NOTES

[1] Part of this report has been the subject of a preliminary communication: S. Terashima, K. Tamoto and M. Sugimori, *Tetrahedron Lett.* **23**, 4107 (1982).

[2] Present address: Sagami Chemical Research Center, 4-4-1, Nishi-Ohnuma, Sagamihara, Kanagawa 229, Japan. All correspondence should be addressed to Sagami Chemical Research Center.

[3a] F. Arcamone, *Lloydia* **40**, 45 (1977); [b] F. Arcamone, *Topics in Antibiotic Chemistry* (Edited by P. G. Sammes), Vol. 2, pp. 99–239. Ellis Horwood, Chichester, England (1978). [c] F. Arcamone, *Anticancer Agents Based on Natural Product Models* (Edited by J. M. Cassady and J. D. Douros), pp. 1–41. Academic Press, New York (1980).

[4] M. B. Naff, J. Plowman and V. L. Narayanan, *Anthracycline Antibiotics* (Edited by H. S. El Khadem), pp. 1–57. Academic Press, New York (1982).

[5a] F. Arcamone, L. Bernardi, P. Giardino, B. Patelli, A. DiMarco, A. M. Casazza, G. Pratesi and P. Reggiani, *Cancer Treat. Rep.* **60**, 829 (1976); [b] F. Arcamone, L. Bernardi, B. Patelli, P. Giardino, A. DiMarco, A. M. Casazza, C. Soranzo and G. Pratesi, *Experientia* **34**, 1255 (1978); [c] F. Arcamone, L. Bernardi, B. Patelli and A. DiMarco, *Ger. Offen.* 2601785 (1976); [d] F. Arcamone, *et al.*, *Japan Kokai Tokkyo Koho JP* 51-98264 (1976); [e] L. Bernardi, P. Giardino, B. Pratesi and F. Arcamone, *Japan Kokai Tokkyo Koho JP* 52-156852 (1977); [f] F. Arcamone, L. Bernardi, P. Giardino and A. DiMarco, *Japan Tokkyo Koho JP* 57-36919 (1982); [g] B. Patelli, L. Bernardi, F. Arcamone and A. DiMarco, *Japan Tokkyo Koho JP* 58-40557 (1983).

[6a] T. R. Kelly, *Ann. Rep. Med. Chem.* **14**, 288 (1979); [b] S. Terashima, *Yuki Gosei Kagaku Kyokai Shi* **40**, 20 (1982).

[7] S. Terashima, S-s. Jew and K. Koga, *Tetrahedron Lett.* 4507 (1977); [b] S. Terashima, S-s. Jew and K. Koga, *Tetrahedron Lett.* 4937 (1978); [c] S-s. Jew, S. Terashima and K. Koga, *Chem. Pharm. Bull.* **27**, 2351 (1979).

[8] R. N. Warrener, P. S. Gee and R. A. Russell, *J. Chem. Soc.* Chem. Commun. 1100 (1981).

[9a] S. Terashima, N. Tanno and K. Koga, *Tetrahedron Lett.* **21**, 2749 and 2753 (1980); [b] N. Tanno and S. Terashima, *Chem. Pharm. Bull.* **31**, 811 and 821 (1983).

[10a] S. Terashima and K. Tamoto, *Tetrahedron Lett.* **23**, 3715 (1982); [b] K. Tamoto and S. Terashima, *Chem. Pharm. Bull.* in press.

[11] D. Domínguez, R. J. Ardecky and M. P. Cava, *J. Am. Chem. Soc.* **105**, 1608 (1983).

[12] D. Domínguez and M. P. Cava, *J. Org. Chem.* **48**, 2820 (1983).

[13] R. C. Gupta, P. A. Harland and R. J. Stoodley, *J. Chem. Soc.* Chem. Commun. 754 (1983).

[14a] M. J. Broadhurst and C. H. Hassall, *J. Chem. Soc.* Perkin I 2227 (1982); [b] M. J. Broadhurst, C. H. Hassall and G. H. Thomas, *J. Chem. Soc.* Perkin I 2239 and 2249 (1982).

[15a] M. Sanz-Burata, J. Irurre-Pérez and S. Juliá-Arechaga, *Afinidad* 693, 698 and 705 (1970); [b] J. J. Plattner and H. Rapoport, *J. Am. Chem. Soc.* **93**, 1758 (1971); [c] J. Casanova, Jr. and E. J. Corey, *Chem. Ind.* 1664 (1961).

[16] Commercially available sample was directly used.

[17] Prepared from natural (2R, 3R)-(+)-tartaric acid according to the reported method.[18]

[18] N. Ando, Y. Yamamoto, J. Oda and Y. Inoue, *Synthesis* 688 (1978).

[19] M. Carmack and C. J. Kelley, *J. Org. Chem.* **33**, 2171 (1968).

[20] P. W. Feit, *J. Med. Chem.* **7**, 14 (1964).

[21] L. F. Wiggins, *J. Chem. Soc.* 13 (1946).

[22] A. H. Haines and C. S. P. Jenkins, *J. Chem. Soc.* Perkin I 273 (1972).

[23a] S. Terashima and K. Tamoto, *Tetrahedron Lett.* **24**, 2589 (1983); [b] K. Tamoto and S. Terashima, *Chem. Pharm. Bull.* in press.

[24] A. S. Kende and J. P. Rizzi, *Anthracycline Antibiotics* (Edited by H. S. El Khadem), pp. 141–166. Academic Press, New York (1982).

[25a] A. S. Kende, Y-g. Tsang and J. E. Mills, *J. Am. Chem. Soc.* **98**, 1967 (1976); [b] A. S. Kende, D. P. Curran, Y-g. Tsay and J. E. Mills, *Tetrahedron Lett.* 3537 (1977).

[26a] T. H. Smith, A. N. Fujiwara, D. W. Henry and W. W. Lee, *J. Am. Chem. Soc.* **98**, 1969 (1976); [b] T. H. Smith, A. N. Fujiwara, W. W. Lee, H. Y. Wu and D. W. Henry, *J. Org. Chem.* **42**, 3653 (1977).

[27] S. D. Kimball, D. R. Walt and F. Johnson, *J. Am. Chem. Soc.* **103**, 1561 (1981).

[28] K. Krohn, *Liebigs Ann. Chem.* 2285 (1981).

[29] P. N. Confalone and G. Pizzolato, *J. Am. Chem. Soc.* **103**, 4251 (1981).

[30] A. S. Kende and J. P. Rizzi, *J. Am. Chem. Soc.* **103**, 4247 (1981).

[31] In the total synthesis of 4-demethoxy-6-deoxyanthracycline, the synthetic scheme similar to ours was reported to exclusively produce $C_{7\alpha}$-hydroxyanthracyclinones in rather low yield. See, S. Penco, F. Angelucci, F. Arcamone, M. Ballabio, G. Barchielli, G. Franceschi, G. Franchi, A. Suarato and E. Vanotti, *J. Org. Chem.* **48**, 405 (1983).

[32] All m.ps were determined with a Büchi 510 m.p. apparatus and are uncorrected. All b.ps are uncorrected. A Büchi GKR-50 apparatus was used for a bulb-to-bulb distillation. IR spectra measurements were performed with a JASCO DS-402G IR spectrometer. NMR spectra were measured with a JEOL FX-100 spectrometer and a JEOL JNM-PS-100 spectrometer. All signals are expressed as ppm downfield from TMS, used as an internal standard (δ value). The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). Mass spectra were taken with a JEOL JMS-01 SG-2 mass spectrometer. Measurements of optical rotations were carried out using a JASCO DI-181 digital polarimeter. All reactions were performed using anhydrous solvents, and the combined organic extracts obtained in each experiment were dried over anhyd. $MgSO_4$, then filtered and concentrated *in vacuo* with a rotary evaporator. Wako Gel C-200 and Merck Silica Gel 60G were used as an adsorbent for column chromatography and preparative thin layer chromatography (PTLC), respectively. The following abbreviations are used for solvents and reagents: AcOH, Me_2CO, MeCN, C_6H_6, $CHCl_3$, CH_2Cl_2, Et_2O, EtOAc, THF, *p*-TsOH.

[33] L. J. Rubin, H. A. Lardy and H. O. L. Fischer, *J. Am. Chem. Soc.* **74**, 425 (1952).

[34a] J. C. Irvine and R. M. Paterson, *J. Chem. Soc.* 898 (1914); [b] H. O. L. Fischer and H. Appel, *Helv. Chim. Acta* **17**, 1574 (1934).