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A GENERAL AND HIGHLY EFFICIENT ASYMMETRIC SYNTHESIS OF OPTICALLY ACTIVE ANTHRACYCLINONES[1]

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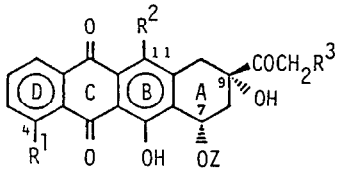
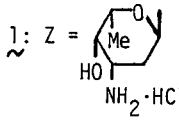
Abstract: The title asymmetric synthesis has been developed by featuring bromolactonization of (-)-acetals, derived from 2-acetyl-3,4-dihydronaphthacene-6,11-diones and (2R,3R)-(+)-N,N,N',N'-tetraalkyltartaric acid diamides, as a key diastereoselective reaction. The produced bromolactone mixtures could be readily converted to the highly optically active key synthetic intermediates of 4-demethoxy- and 11-deoxy-4-demethoxyanthracyclinones.

The anthracycline antibiotics, adriamycin (1a) and daunorubicin (1b), place leading positions of anticancer agents because of their prominent activity against various types of human cancers.[2] While their utilization for cancer chemotherapy is restricted by various undesirable side effects, most notably cardiotoxicity,[2] more improved therapeutic indices can be foreseen for recently discovered natural 11-deoxy-anthracyclines (1e,f)[3] and ingeniously explored unnatural 4-demethoxy-[2,4] and 11-deoxy-4-demethoxyanthracyclines[5] (1c,d and 1g,h).

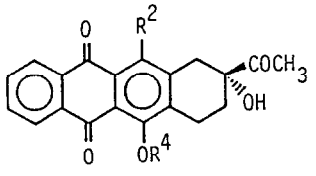
Numerous syntheses of optically active natural and unnatural 11-hydroxy-anthracyclinones (2a-d), the aglycones of 1a-d, have hitherto been reported by employing asymmetric synthesis and optical resolution.[6,7] However, a general synthetic method being applicable not only to optically active 11-hydroxy-anthracyclinones (2a-d) but also to their 11-deoxy congeners (2e-h), seems to be still lacking.



	R^1	R^2	R^3		R^1	R^2	R^3
a	OMe	OH	OH	e	OMe	H	OH
b	OMe	OH	H	f	OMe	H	H
c	H	OH	OH	g	H	H	OH
d	H	OH	H	h	H	H	H



2: Z = H



dl- or (R)-3

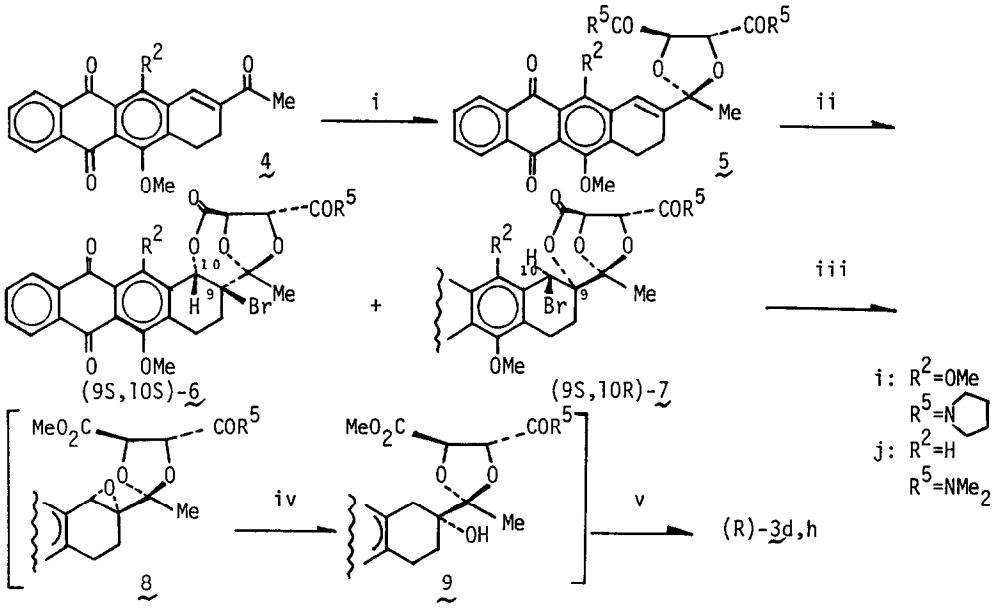
	R^2	R^4
d	OH	H
h	H	H
i	OMe	Me
j	H	Me

Previously, the authors reported a novel asymmetric synthesis of the AB ring system of optically active 11-hydroxy-anthracyclinones (2a-d) in which bromolactonization of the (-)-acetal derivatives constituted the key diastereoselective reactions.[8] The AB ring system obtained in >95% ee can be elaborated to optically active 2a-d by annulating the CD ring.[6,9] Considering various notable aspects previously delineated,[8] application of the developed asymmetric synthesis to preparation of optically active (R)-7-deoxy- and (R)-7,11-dideoxy-4-demethoxydaunomycinone ((R)-3d and (R)-3h) was attempted.

We have now succeeded in preparing highly optically active tetracyclic α-hydroxy ketones ((R)-3d,h) which are advanced key synthetic intermediates of unnatural 4-demethoxy- and 11-deoxy-4-demethoxyanthracyclinones (2c,d and 2g,h), from tetracyclic 2-acetyl-3,4-dihydronaphthacen-6,11-dione derivatives (4).

The starting material (4i)[10] required for the asymmetric synthesis of (R)-3d could be readily prepared from dl-3d[6,9,11] by dehydration[12] ($(CF_3CO)_2O$-collidine, 77%) followed by methylation (NaH-Bu_4NBr-Me_2SO_4 in THF, 82%). The dehydration product of dl-3d, 2-acetyl-5,12-dihydroxy-3,4-dihydronaphthacene-6,11-dione,[10] can be also synthesized according to the reported method.[13] Acetalization of 4i with trimethoxymethane followed by transacetalization of the crude dimethylacetal with (2R,3R)-(+)-N,N:N',N'-bistetramethylenetartaric acid diamide,[8] gave (-)-acetal ((-)-5i)[10] in 89% yield based on 4i. Treatment of (-)-5j under the same bromolactonization condition as that developed previously[8] afforded a mixture of the bromolactones in 78% yield. Trituration of the mixture with chloroform-ether gave the predominantly formed seven-membered bromolactone ((9S,10S)-6j) as a yellow powder.[10] The crude unstable six-membered bromolactone ((9S,10R)-7i) could be also isolated as a yellow solid by concentration of the mother liquor of trituration in vacuo, followed by column chromatography (SiO_2: PhH-EtOAc 2:1). Structures of (9S,10S)-6i and (9S,10R)-7j could be tentatively assigned based on their spectral data, and successful preparation of highly optically active (R)-3d from the bromolactone mixture (vide infra). NMR spectrum of the bromolactone mixture clearly disclosed that no detectable amounts of the undesired bromolactones bearing (9R,10R)- and (9R,10S)-configurations and being diastereomeric to (9S,10S)-6i and (9S,10R)-7j, were produced by the bromolactonization of (-)-5j. Formation ratio of (9S,10S)-6j to (9S,10R)-7i could be roughly estimated as 6:1 by integration of the C_{10}-methine signals observed in the NMR spectrum ((9S,10S)-6i: 6.04 ppm (J= 2.0 Hz); (9S,10R)-7i: 5.60 ppm (J= 2.1 Hz)). Direct alkaline treatment converged the mixture of (9S,10S)-6i and (9S,10R)-7i into the epoxide (8j), which without isolation was hydrogenated to give the tertiary alcohol (9j). Acidic removal of the acetal group derived from the chiral source, followed by demethylation, produced (R)-3d,[10] mp 215-218.5°C, $[\alpha]_D^{20}$ -90.4° (c 0.104, $CHCl_3$) and $[\alpha]_D^{20}$ -20.1° (c 0.189, $CHCl_3$-MeOH 1:1), 94% ee,[15] in 68% yield based on the bromolactone mixture. Recrystallization of this sample readily afforded optically pure (R)-3d.[10]

The developed reaction scheme was next applied to the asymmetric synthesis of (R)-7,11-dideoxy-4-demethoxydaunomycinone ((R)-3h). The reaction substrate (4j)[10] was prepared from dl-3h[16] by sequential methylation (Me_2SO_4-K_2CO_3 in Me_2CO, 87%) and dehydration ($SOCl_2$-pyridine, 50%) of the methyl ether (dl-3j).[10] Treatment of 4j in a similar fashion to that described for 4j gave (-)-5j[10] in 77% yield based on 4j. Subjection of (-)-5j to the bromo-



i) For 4i: $CH(OMe)_3$-dl-camphorsulfonic acid (CSA) in MeOH, rt, then, (2R,3R)-(+)-N,N:N',N'-bistetramethylenetartaric acid diamide (2.0 equiv.)-molecular sieves (MS) 4A-dl-CSA in PhH, reflux. For 4j: $CH(OMe)_3$-pyridinium p-toluenesulfonate (PPTS) in CH_2Cl_2-MeOH, rt, then, 45°C, then, (2R,3R)-(+)-N,N,N',N'-tetramethyltartaric acid diamide (2.0 equiv.)-PPTS in PhH, reflux. ii) MeCONHBr (3.0 equiv. for 5i, 4.0 equiv. for 5j), in DMF-H_2O (100:1), rt. iii) anhyd K_2CO_3 in MeOH, rt. iv) H_2-Pd/C in MeOH, 1 atm, rt. v) concd HCl in EtOH, then, $AlCl_3$ in PhH.

lactonization gave a mixture of the bromolactones mainly consisting of (9S,10S)-6j and (9S,10R)-7j in 85% yield, from which the predominantly produced seven-membered bromolactones ((9S,10S)-6j)[10] could be isolated in a pure state by recrystallization. Formation ratio of (9S,10S)-6j to (9S,10R)-7j was similarly estimated as 5~6:1 based on the NMR spectrum. The same four successive treatments of the bromolactone mixture as those described for the 11-hydroxy series, produced (R)-3h,[17] mp 202-204.5°C, $[\alpha]_D^{20}$ -32.7° (c 0.104, $CHCl_3$) and $[\alpha]_D^{20}$ +17.3° (c 0.104, $CHCl_3$-MeOH 1:1), >99% ee,[15] by way of 8j and 9j in 49% overall yield. Optically pure (R)-3h[10] could be obtained by recrystallization of this sample.

The highly diastereoselective bromolactonization reactions giving rise to the mixtures of (9S,10S)-6i,j and (9S,10R)-7i,j, can be best explained by the reaction mechanism similar to that proposed for the asymmetric synthesis of the AB ring system.[8] Being different from the previous case,[8] formation of appreciable amounts of the six-membered bromolactones ((9S,10R)-7i,j) was observed. This is presumably due to the anthraquinone groups involved in 5i,j, which may destabilize creation of the cationic nature at the C_{10}-position during the bromolactonization.

Similarly to asymmetric synthesis of the AB ring system,[8] various notable merits such as uses of readily available reaction substrates, chiral sources, and reagents, mild reaction conditions, and high optical yields, can be also recognized for this successful preparation

of (R)-3d,h from 4i,j. Accordingly, the developed asymmetric synthesis is anticipated as one of the most practical and general synthetic methods of various optically active anthracyclinones including their 11-deoxy congeners.

References and Notes

1) This paper is dedicated to Prof. Shun-ichi Yamada on the occasion of his 70th birthday.
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10) Following melting points (recrystallization solvents) and optical rotations were recorded: 4j, mp 202.5-204°C ($CHCl_3$-MeOH); 2-acetyl-5,12-dihydroxy-3,4-dihydronaphthacene-6,11-dione, mp 245-246°C ($CHCl_3$-EtOH) (lit.,[13] mp 235-237°C); (-)-5j, mp 148.5-150.5°C ($CHCl_3$-Et_2O), $[\alpha]_D^{20}$ -20.4° (c 1.02, $CHCl_3$); (9S,10S)-6j, mp 217-219°C ($CHCl_3$-Et_2O), $[\alpha]_D^{20}$ -263° (c 0.104, $CHCl_3$); (9S,10R)-7j, $[\alpha]_D^{20}$ +295° (c 0.124, $CHCl_3$); (R)-3d, mp 219-220°C (PhH), $[\alpha]_D^{20}$ -90.9° (c 0.099, $CHCl_3$) and $[\alpha]_D^{20}$ -20.0° (c 0.190, $CHCl_3$-MeOH 1:1) (lit.,[9] mp 218-219.5°C, $[\alpha]_D^{20}$ -90.0° (c 0.106, $CHCl_3$), lit.,[14] $[\alpha]_D$ -20.0° (c 0.18, $CHCl_3$-MeOH 1:1)); 4j, mp 241.5-243°C ($CHCl_3$-MeOH); dl-3j, mp 209-209.5°C ($CHCl_3$-MeOH); (-)-5j, mp 132.5-135.5°C (Et_2O), $[\alpha]_D^{20}$ -14.6° (c 1.03, $CHCl_3$); (9S,10S)-6j, mp 238-239.5°C ($CHCl_3$-Et_2O), $[\alpha]_D^{20}$ -103° (c 0.105, $CHCl_3$); (R)-3h, mp 204.5-206.5°C (PhH), $[\alpha]_D^{20}$ -35.3° (c 0.102, $CHCl_3$) and $[\alpha]_D^{20}$ +16.0° (c 0.100, $CHCl_3$-MeOH 1:1).
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15) The optical yield of this sample was determined by measuring the NMR spectrum of the methyl ether ((R)-3j,j) derived from (R)-3d,h by usual methylation (Me_2SO_4-K_2CO_3 in Me_2CO), in the presence of the chiral shift reagent ($Eu(hfc)_3$).
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17) The absolute configuration of this sample was assumed to belong to (R)-series based on the results obtained for the asymmetric synthesis of (R)-3d.

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