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Novel Syntheses of Optically Active 4-Demethoxyanthracyclinones Carrying a Hydroxymethyl or a Carbamoyloxymethyl Group at the C_9-Position

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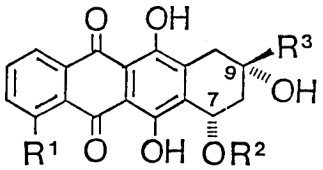
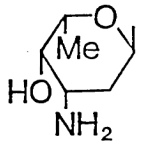
The title compounds were effectively synthesized by chemoselective reduction of (R)-methyl 2,5,12-trihydroxy-6,11-dioxo-1,2,3,4-tetrahydronaphthacene-2-carboxylate to the corresponding (R)-alcohol with lithium tri-t-butoxyaluminium hydride, followed by stereoselective $C_{7\alpha}$-hydroxylation (the anthracycline numbering) and urethane formation.

Over the past decade, numerous synthetic efforts have been devoted to the anthracycline antibiotics represented by adriamycin (**1a**) and daunorubicin (**1b**).[1] Especially, in the hope of finding unnatural anthracyclines which can show more improved therapeutic indices than **1a,b**, various congeners have been prepared by chemical synthesis or by modification of fermentation-derived anthracyclines.[1,2]

Among synthetically elaborated analogues of **1a,b**, 4-demethoxy-9-deacetyl-9-hydroxymethyldaunorubicin (**1c**) and 4-demethoxy-9-deacetyl-9-carbamoyloxymethyl-daunorubicin such as **1d** originally explored by Broadhurst et al.,[3] attract our attention because of their prominent anticancer activity well-compared with that of well-known 4-demethoxyadriamycin (**1e**) and 4-demethoxydaunorubicin (**1f**).[4,5] While various efficient synthetic routes have been explored for the aglycones (**2e,f**) of **1e,f**,[1,6] a limited number of methods is only available for the aglycones (**2c,d**) of **1c,d** which carry a hydroxymethyl or a carbamoyloxymethyl group at the C_9-position (the anthracycline numbering).[3,7]

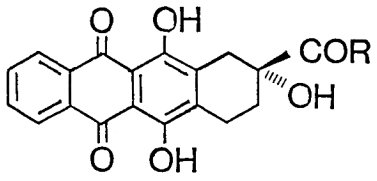


1 : R^2 =



2 : R^2 = H

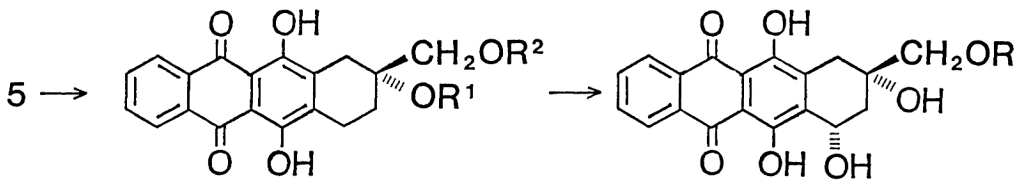
	R^1	R^3
a	OMe	$COCH_2OH$
b	OMe	COMe
c	H	CH_2OH
d	H	$CH_2OCONHPh$
e	H	$COCH_2OH$
f	H	COMe



3 : R = OH
4 : R = Me
5 : R = OMe

It was previously reported that (R)-2,5,12-trihydroxy-6,11-dioxo-1,2,3,4-tetrahydronaphthacene-2-carboxylic acid (**3**) produced by optical resolution of the readily available racemic acid,[6] could be directly converted to the corresponding (R)-methyl ketone (**4**), the key synthetic intermediate of **2e,f**.[6] We wish to report here that (R)-methyl 2,5,12-trihydroxy-6,11-dioxo-1,2,3,4-tetrahydronaphthacene-2-carboxylate (**5**) obtainable from **3**,[6] can be reduced to the corresponding (R)-alcohol (**6**) in a highly chemoselective manner, and that **6** can be readily elaborated to **2c,d** by sequential stereoselective $C_{7\alpha}$-hydroxylation and urethane formation.

In order to produce **6** from **5**, an efficient reducing agent was sought which can chemoselectively reduce the methyl ester without reduction of the 5,12-dihydroxy-6,11-dioxo-1,2,3,4-tetrahydronaphthacene system. After several unsuccessful attempts,[8] the reduction with lithium tri-t-butoxyaluminum hydride in dimethyl sulfoxide was found to be quite promising. Thus, treatment of **5**,[6] mp 213-214°C and $[\alpha]_D^{20}$ -60.0° (c 0.110, $CHCl_3$)[lit.,[6] mp 210.5-211.5°C and $[\alpha]_D^{20}$ -60.0° (c 0.10, $CHCl_3$)], with lithium tri-t-butoxyaluminum hydride[10] (15-25 equiv.) in dimethyl sulfoxide[11] at room temperature for 5 h, followed by silylation with 4-t-butyldimethylsilyloxy-3-penten-2-one[12] in N,N-dimethylformamide in the presence of p-toluenesulfonic acid at room temperature and separation by column chromatography (SiO_2, $CHCl_3$-EtOAc 30:1), gave (R)-silyl ether (**7**) (55%, 2 steps), mp 158.5-159°C and $[\alpha]_D^{20}$ -40.7° (c 0.059, $CHCl_3$). While **6** was isolated as its silyl ether (**7**) because of its extremely low solubility to usual organic solvents, it could be also purified in a form of its acetonide (**8**). Namely, treatment of the crude reduction product with 2,2-dimethoxypropane in the



6 : $R^1 = R^2 = H$
7 : $R^1 = H$, $R^2 = SiMe_2Bu\text{-}t$
8 : $R^1, R^2 = CMe_2$

9 : $R = SiMe_2Bu\text{-}t$
2c : R = H
2d : R = CONHPh

presence of dl-camphorsulfonic acid in a mixture of acetone and tetrahydrofuran, produced **8**[13] (55%, 2 steps), mp 221.5-222.5°C and $[\alpha]_D^{20}$ -52.0° (c 0.050, $CHCl_3$) [lit.,[7] mp 232-234°C and $[\alpha]_D$ -52° (c 0.03, $CHCl_3$)]. In this reduction, the starting ester (**5**) was always recovered in 26-34 % yield. Regeneration of **6**,[13] mp 264.5-266.5°C and $[\alpha]_D^{20}$ -52.0° (c 0.050, dioxane) [lit.,[7] mp 235-238°C and $[\alpha]_D$ -32° (c 0.062, dioxane)], from **7** or **8** was accomplished quantitatively by treating with concd hydrochloric acid in tetrahydrofuran at room temperature. However, taking into account the low solubility of **6**, the $C_{7\alpha}$-hydroxylation was directly attempted using **7**.

Similarly to the reported method,[14] bromination of **7** was examined with bromine in carbon tetrachloride under irradiation with a 60W tungsten lamp for 2 h, and the formed bromide was treated with 0.3 mol dm^{-3} sodium hydroxide solution for 0.5 h, giving the $C_{7\alpha}$-hydroxylated silyl ether (**9**) (43%, 2 steps), mp 138-147°C and $[\alpha]_D^{20}$ +135° (c 0.055, $CHCl_3$), after purification by column chromatography (SiO_2, $CHCl_3$, then, $CHCl_3$-EtOAc 30:1). While a small amount of the starting material (**7**) was recovered (8%), formation of the undesired $C_{7\beta}$-epimer could not be detected by the NMR spectrum of the crude reaction product. Highly stereoselective formation of **9** can be explained by the attack of the hydroxide anion hydrogen-bonded with the $C_{9\alpha}$-hydroxyl group.[14] Deprotection of **9** with aqueous hydrofluoric acid in acetonitrile gave a quantitative yield of **2c**[13], a reddish orange solid, mp 201.5-204.5°C and $[\alpha]_D^{20}$ +167° (c 0.024, dioxane), $[\alpha]_D^{30}$ +111° (c 0.052, tetrahydrofuran) [lit.,[3b] mp 212-214°C and $[\alpha]_D^{20}$ +131.3° (c 0.1, dioxane); lit.,[7] mp 230°C and $[\alpha]_D$ +95° (c 0.05, tetrahydrofuran)].

Selective urethane formation could be readily achieved by allowing **2c** to react with phenylisocyanate in pyridine at room temperature. The urethane (**2d**) obtained as an orange solid (52%), showed mp 222-223°C and $[\alpha]_D^{20}$ +121° (c 0.053, dioxane) [lit.,[3] mp 225-226°C and $[\alpha]_D^{20}$ +136.0° (c 0.05, dioxane)]. The uses of other isocyanates would similarly afford the corresponding urethanes, being useful as aglycones of various 4-demethoxy-9-deacetyl-9-carbamoyloxymethyldaunorubicins.[3]

As described above, we have succeeded in developing the novel synthetic route to **2c,d**. Considering its directness and simplicity being obviously superior to those of the reported methods,[3,7] the explored scheme may hold promise as a practical synthetic route to these unnatural anthracyclinones.

References

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3) M. J. Broadhurst, C. H. Hassal, and G. J. Thomas, Eur. Patent 44954; Japan Kokai Tokkyo Koho, JP 57-53497 and JP 59-80692.
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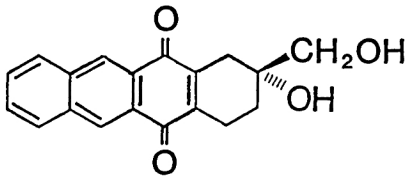
5) Y. Kimura, M. Suzuki, T. Matsumoto, R. Abe, and S. Terashima, Bull. Chem. Soc. Jpn., 59, 423 (1986) , and references cited therein.
6) Y. Kimura, M. Suzuki, T. Matsumoto, R. Abe, and, S. Terashima, Bull. Chem. Soc. Jpn., 59, 415 (1986) , and references cited therein.
7) For other synthesis of **2c** in which the chiral A ring was constructed from D-lactone, see, F. Bennaui, J-C. Folient, M. Kochi, and C. Monneret, Tetrahedron, 40, 4669 (1984).
8) For example, when **5** was treated with lithium aluminum hydride in tetrahydrofuran, the ester group and the 5,12-dihydroxy-6,11-dioxo-1,2,3,4-tetrahydronaphthacene system were found to be simultaneously reduced to afford 2-hydroxy-2-hydroxymethyl-5,12-dioxo-1,2,3,4-tetrahydronaphthacene (**10**) in 68% yield. According to the process similar to that reported,[9] **10** was transformed to **6** (isolated as **8**, see the text) in 34% overall yield by sequential acetylation (Ac_2O-Py-DMAP), reductive acetylation (Zn-Ac_2O), oxidation (CrO_3 in 80% AcOH), and hydrolysis (aq NaOH). Reduction of **5** with diisobutylaluminum hydride in toluene or with sodium bis(2-methoxyethoxy)aluminum hydride in toluene gave complex mixtures of products, in which **5** could not be detected by TLC analysis.



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10) Prepared as a white powder by adding 3.0 equiv. of t-butyl alcohol to a suspension of lithium aluminum hydride in ether and by concentrating the mixture in vacuo.
11) This reduction was found to be highly dependent on a reaction solvent. Thus, the reduction carried out in tetrahydrofuran, gave **6** (isolated as **7**, see the text) and **10** in 46% and 24% yields, respectively, with 21% recovery of **5**. When N,N-dimethylformamide was used as a solvent, a 19% yield of **6** (isolated as **7**) was obtained with 51% recovery of **5**.
12) T. Veysoglu and L. A. Mitscher, Tetrahedron Lett., 22, 1299, 1303 (1981).
13) The NMR spectrum of this sample was identical with that reported.[7]
14) K. Tamoto, M. Sugimori, and S. Terashima, Tetrahedron, 40, 4617 (1984).

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