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AN EFFICIENT ASYMMETRIC SYNTHESIS OF 11-DEOXYANTHRACYCLINONE[1]

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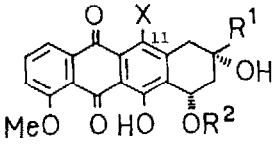
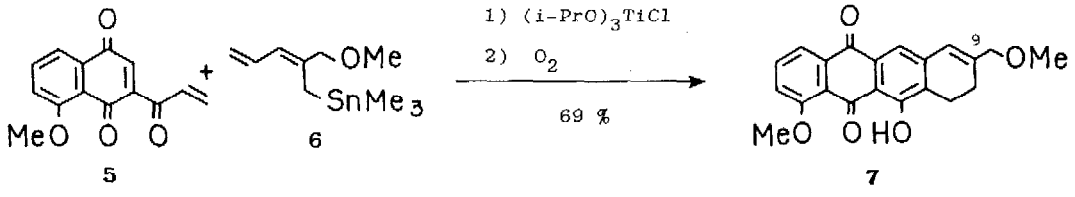
(7S,9S)-(+)-11-Deoxyanthracyclinone **4b** is synthesized in a high optical yield (96 %ee) by the Sharpless asymmetric epoxidation of the tetracyclic allylalcohol 9, which is readily prepared via the tandem Michael/Diels-Alder reaction.

During continuous efforts to obtain the more efficacious therapeutic agents against tumours, 11-deoxyanthracyclines such as 11-deoxydaunomycin, 11-deoxyadriamycin, aclacinomycin, and nogalamycin have been found to be a new group with high antitumour activities and reduced toxicities.[2-4] A major problem for the synthesis of 11-deoxyanthracyclinones is how to arrange their functional groups properly on account of their decreased molecular symmetry. As one of the most satisfactory solutions to this problem, we have already reported the route including tandem Michael/Diels-Alder reaction.[5]



1 ; X = OH, R^1 = $COCH_3$ **3** ; X = H , R^1 = $COCH_3$ **a** ; R^2 = daunosaminyl
2 ; X = OH, R^1 = CH_2OH **4** ; X = H , R^1 = CH_2OH **b** ; R^2 = H

In recent years, an intense interest in this field is centering to the asymmetric synthesis.[4c,6] In this communication, we describe an efficient asymmetric synthesis of the 11-deoxydaunomycinone analogue **4b** from the substrate **7**[5c] readily synthesized by our method. Arcamone and his co-workers have prepared a modified daunomycin, 9-deacetyl-9-hydroxymethyl-daunomycin **2a**,[7] which is found as active as the parent daunomycin **1a**. Therefore, a facile synthesis of its 11-deoxy congener **4a** or the aglycon **4b** is required.

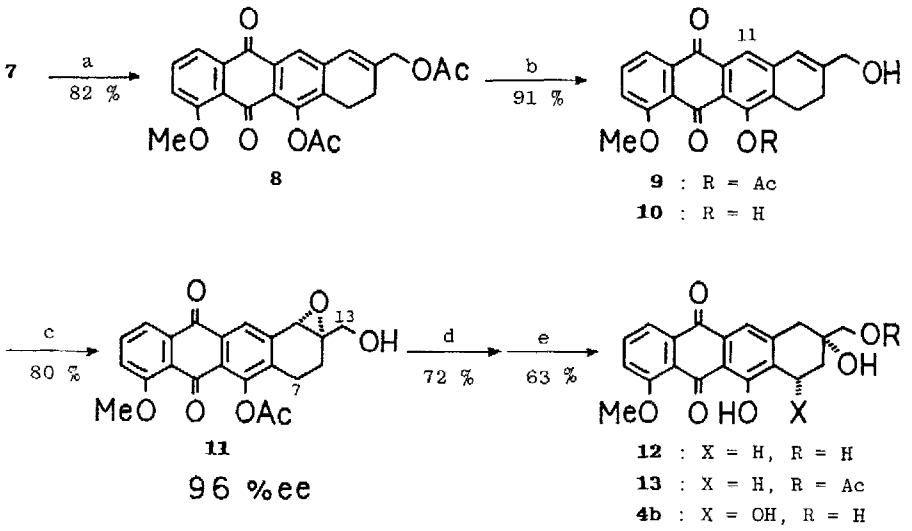


5 **6** **7**

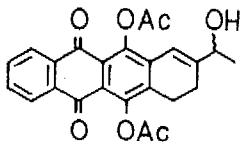
Possessing a methyl-protected allylic alcohol moiety, the tetracyclic quinone **7**, which was prepared in 69 % yield by means of Lewis acid mediated tandem Michael/Diels-Alder reaction of pentadienyltin 6 with acryloylquinone 5, has potentialities to introduce a chirality into its 9-position by asymmetric epoxidation. On the way to the optically active anthracyclinone **4b** from **7**, there were mainly three problems: (1) selective demethylation of the allylic methyl ether,[8] (2) selective protection of the phenolic hydroxyl group,[9] and (3) enantioselective epoxidation in a high yield.[10]

As depicted in Scheme I, the problems were satisfactorily solved and optically active **4b** was obtained in pure form. First, the selective demethylation of **7** successfully proceeded by use of $HClO_4$ in acetic anhydride and dichloromethane at 0 °C for 5 min to give the corresponding allyl acetate **8** in 82 % yield. The phenolic hydroxyl group was simaltaneously acetylated, and the phenolic methyl ether remained intact. Methanolysis under acidic conditions[11] conveniently converted the diacetate **8** into the monoacetyl allylic alcohol **9** in 91 % yield. Thus, selective protection of the phenolic hydroxyl group was achieved.

Scheme I.



[a] $HClO_4$ in Ac_2O-CH_2Cl_2, 0 °C, 5 min. [b] H_2SO_4 in MeOH-acetone, reflux, 4 h. [c] $(i\text{-PrO})_4Ti$, (+)-DET, t-BuOOH, and MS 4A in CH_2Cl_2, -20 °C, 15 h. [d] $Na_2S_2O_4$ and NaOH in H_2O, 0 °C, 1 h. [e] 1) Ac_2O and pyridine in CH_2Cl_2, room temperature, 12 h; 2) Br_2(1.75 equiv)/light in CCl_4, room temperature, 1 h; 3) NaOH in H_2O, 0 °C, 1 h.



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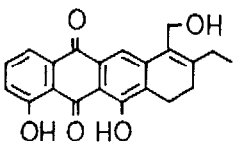

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Asymmetric epoxidation[12] of 9 prosperously proceeded with markedly high optical (96 %ee) and chemical (80 %) yields to give 11 by employing (+)-diethyltartrate (1.2 equiv), $(i\text{-PrO})_4Ti$ (1.0 equiv), and t-BuOOH (2.2 equiv) at -20 °C. The ee of 11 was determined by 400 MHz ^1H NMR of its corresponding (R)-MTPA ester. This demonstrates that the tetracyclic allylic alcohol 9 was much more suitable for the asymmetric epoxidation than the related substrates, 14[6a] and 15[6b].

Reductive ring opening of 11 in an alkaline aqueous solution of $Na_2S_2O_4$ gave the corresponding diol (-)-12[13] in 72 % yield.

Stereoselective introduction of a hydroxyl group to the 7-position of 12 was performed by a similar method to the reported one[14] after acetyl protection[15] of the primary alcohol 12 to 13. The 11-deoxyanthracyclinone (+)-4b[16] was thus obtained in 27 % total yield from the tetracyclic quinone 7 with high enantiomeric purity.

It is advantageous in respect of prevention against racemization that the chirality at the 9-position is induced very efficiently into a tetracyclic anthracyclinone system at the latest step. Thus, the present method is one of the most promising routes to optically active 11-deoxyanthracyclinones.

References and Notes

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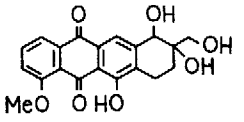
8. The use of more easily deprotective groups (e.g. methoxymethyl ether) was not successful owing to synthetic difficulty in preparing the corresponding tin reagent.
9. The presence of the unprotected hydroxyl group at the 6-position impairs the efficiency in the asymmetric epoxidation; refs. 6a, 6b, and Rizzi, J.P.; Kende, A.S. ref. 4c, p. 4693.
10. The previously reported ee values in similar tetracyclic systems were 56 % and 53±2 % for **14**[6a] and **15**[6b] respectively. In bicyclic AB-ring systems, high ee values have been obtained.[61,m]
11. Hydrolysis of the diacetate **8** under basic conditions gave diol **10**, of which Sharpless epoxidation was very slow at -20 °C even in the presence of a large excess amount of the reagents (5-10 equiv to the substrate). Most of the allylic alcohol **10** was recovered and only a trace amount of the triol (in ring A) **16** was obtained under the similar conditions reported.[6b]



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13. (-)-**12**: mp 245-250 °C (dec.); $[\alpha]_D$ -10.6° (c 0.52, dioxane); MS m/z 354 (M^+); ^1H NMR ($CDCl_3$) δ 1.81 (dt, J=13.1, 7.9 Hz), 2.03 (dt, J=13.1, 6.7 Hz), 2.95 (m, 4H), 3.62 (s, 2H), 4.08 (s, 3H), 7.36 (d, J=7.9 Hz), 7.53 (s), 7.74 (dd, J=8.3, 7.9 Hz), 7.97 (d, J=7.9 Hz), 13.41 (s).
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15. Protection by more labile trifluoroacetyl group resulted in decreased stereoselectivity, because the ester moiety was hydrolyzed so rapidly that the resulting hydroxyl group directed the 7-hydroxyl group to the opposite direction.
16. (+)-**4b**: mp 224-228 °C (dec.); $[\alpha]_D$ +126° (c 0.15, dioxane); MS m/z 370 (M^+); ^1H NMR ($CDCl_3$) δ 1.87 (dd, J=14.7, 4.8 Hz), 2.26 (br), 2.52 (dt, 14.7, 2.0 Hz), 2.80 (d, J=17.5 Hz), 3.06 (dt, J=17.5, 2.0 Hz), 3.42 (br), 3.55 (d, 10.9 Hz), 3.67 (d, 10.9 Hz), 4.08 (s, 3H), 4.15 (s), 5.38 (m), 7.38 (d, 8.3 Hz), 7.59 (s), 7.76 (dd, 8.3, 7.9 Hz), 7.97 (d, 7.9 Hz), 13.65 (s).

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