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A Novel Enantiocontrolled Synthesis of (+)-9-Deacetyl-9-(hydroxymethyl)-4-demethoxydaunomycinone

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An enantiocontrolled synthesis of (+)-9-deacetyl-9-(hydroxymethyl)-4-demethoxydaunomycinone has been achieved via asymmetric introduction of the 9-hydroxyl group as a key step by catalytic Sharpless epoxidation.

The anthracycline antibiotics, daunorubicin and doxorubicin, are widely used for cancer chemotherapy. Due to various undesirable side effects, such as dose-related cardiotoxicity, synthesis of new active and less-toxic anthracyclines has been of considerable interest, and extensive efforts have been devoted to the syntheses of optically active anthracyclinones. We wish to report an efficient synthesis of (+)-9-deacetyl-9-(hydroxymethyl)-4-demethoxydaunomycinone (1)[1] through the introduction of the 9-hydroxyl by catalytic Sharpless epoxidation[2] of allylic alcohol.

The key step in this synthesis, an asymmetric epoxidation, was achieved by treatment of bromo allylic alcohol 2[3] with t-BuOOH (1.2 equiv.) in the presence of $Ti(i\text{-}PrO)_4$ and L-(+)-dimethyl tartrate (0.2 equiv. each) in CH_2Cl_2. The optically active bromo epoxy alcohol 4[4] was obtained in 85% yield (91% ee),[5] mp 88-89 °C (decomp), $[\alpha]_D^{20}$ -103.6° ($CHCl_3$). The stereochemistry of 4 was established at the later stage. On the other hand, epoxy alcohol 5 was unstable under the condition of Sharpless epoxidation of 3. Regioselective reduction of 4 with DIBAH in Et_2O yielded vicinal diol 6 in 95% yield, mp 139-140 °C, $[\alpha]_D^{20}$ -18.9° ($CHCl_3$), which was converted to acetonide 7 in 93% yield, mp 158.5-159 °C, $[\alpha]_D^{20}$ -8.18° ($CHCl_3$). The absolute stereochemistry at the C-2 position of 7 was established as S-configuration by X-ray crystallographic analysis. The acetonide 7 was successfully oxidized to bromoquinone 8 with AgO[6] in 6 M HNO_3 in an almost quantitative yield, mp >125 °C (sublimed), $[\alpha]_D^{20}$ -52° ($CHCl_3$). Conversion of 8 to tetraacetate 13 was carried out by the sequences of condensation of 8 with 9 (LDA, THF, 78% yield), oxidation [$Pb(OAc)_4$, CH_2Cl_2-AcOH, 81% yield], removal of protecting groups (CF_3CO_2H, H_2O, 91% yield) and acetylation (Ac_2O, Py, 76% yield).[4] Bromination[7] of 13 followed by hydrolysis with 10% NaOH-THF gave (+)-9-deacetyl-9-(hydroxymethyl)-4-demethoxydaunomycin (1), mp 228-230 °C, $[\alpha]_D^{20}$ 92° (THF) [lit[1] mp 230 °C, $[\alpha]_D$ 95° (THF)] and trans isomer 14[4] in yields of 18 and

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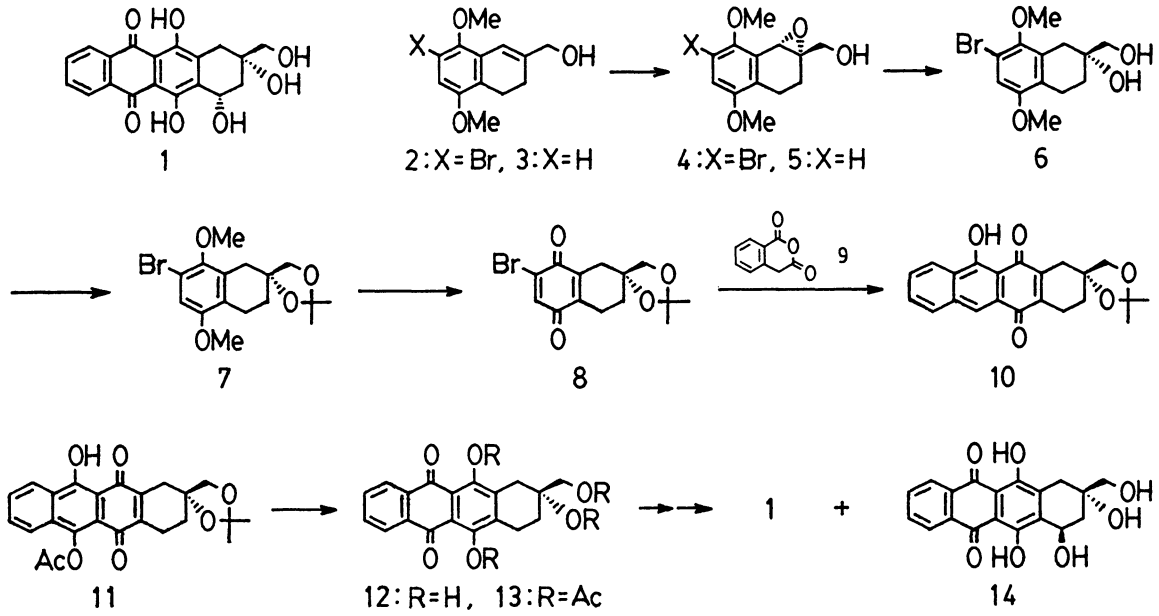
5%, respectively.



The present synthesis of 1 having both of the chiral hydroxymethyl and hydroxyl groups provides a new entry to optically active anthracyclinones.

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References

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2) M. Sodeoka, T. Iimori, and M. Shibasaki, Tetrahedron Lett., 26, 6497 (1985) and references cited therein.
3) Compound 2, mp 93-94 °C, was prepared from 1,4-dimethoxybenzene and succinic anhydride by seven steps in 35% overall yield.
4) 4: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.64-1.72(1H m, H-3), 1.95(1H broad dd, J=4 and 8 Hz, OH), 2.24-2.33(1H m, H-3'), 2.33(1H m, H-4), 2.99(1H m, H-4'), 3.78 and 3.86(each 3H s, OMe), 3.84(1H dd, J=4 and 13 Hz, CH_2OH), 3.98(1H dd, J=8 and 13 Hz, CH_2OH), 4.35(1H s, H-1) and 7.00(1H s, H-6). 10: mp 229-230 °C, $[\alpha]_D^{10}$ -64.9° ($CHCl_3$). 13: $[\alpha]_D^{20}$ -24.3° ($CHCl_3$). 15: mp 206-208 °C, $[\alpha]_D^{20}$ -104° (THF).
5) The enantiomeric purity was calculated from integral value of C-1 methine proton of ^{1}H-NMR spectrum using chiral shift reagent, Eu(hfc)$_3$.
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