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An Approach to Anthracycline Synthetic Intermediate from Novel Glycerol-related Chiral Pool†

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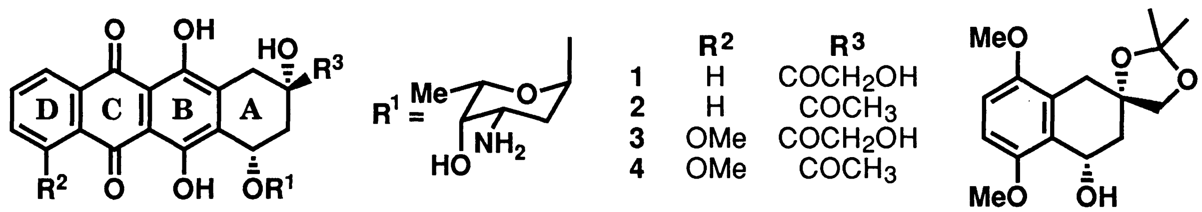
A key-intermediate of synthetic anthracycline, (+)-(1*S*,2*S*)-1,3-dihydroxy-3,3'-O-isopropiridene-3-(hydroxymethyl)-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene was synthesized from optically active 2-substituted glycerol monoacetate which was prepared via enantioselective enzymatic hydrolysis of a prochiral 2-substituted glycerol derivative.

4-Demethoxyadriamycin (**1**) and 4-demethoxydaunorubicin (**2**), semisynthetic analogues of anthracycline, are known to be more effective as antineoplastic agents than naturally occurring anthracycline such as adriamycin (**3**) and daunorubicin (**4**).[1,2] Since pharmaceutical activities of these compounds strictly depend on the chirality at C-9, a number of asymmetric syntheses of AB ring synthons have been reported.[3] We wish to add a new entry to the construction of this ring system starting from a building block which is available in large scale by enzymatic hydrolysis.



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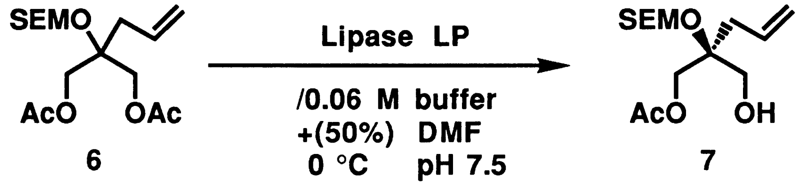
†Dedicated to Professor Emeritus Osamu Simanura of The University of Tokyo on the occasion of his 80th birthday.

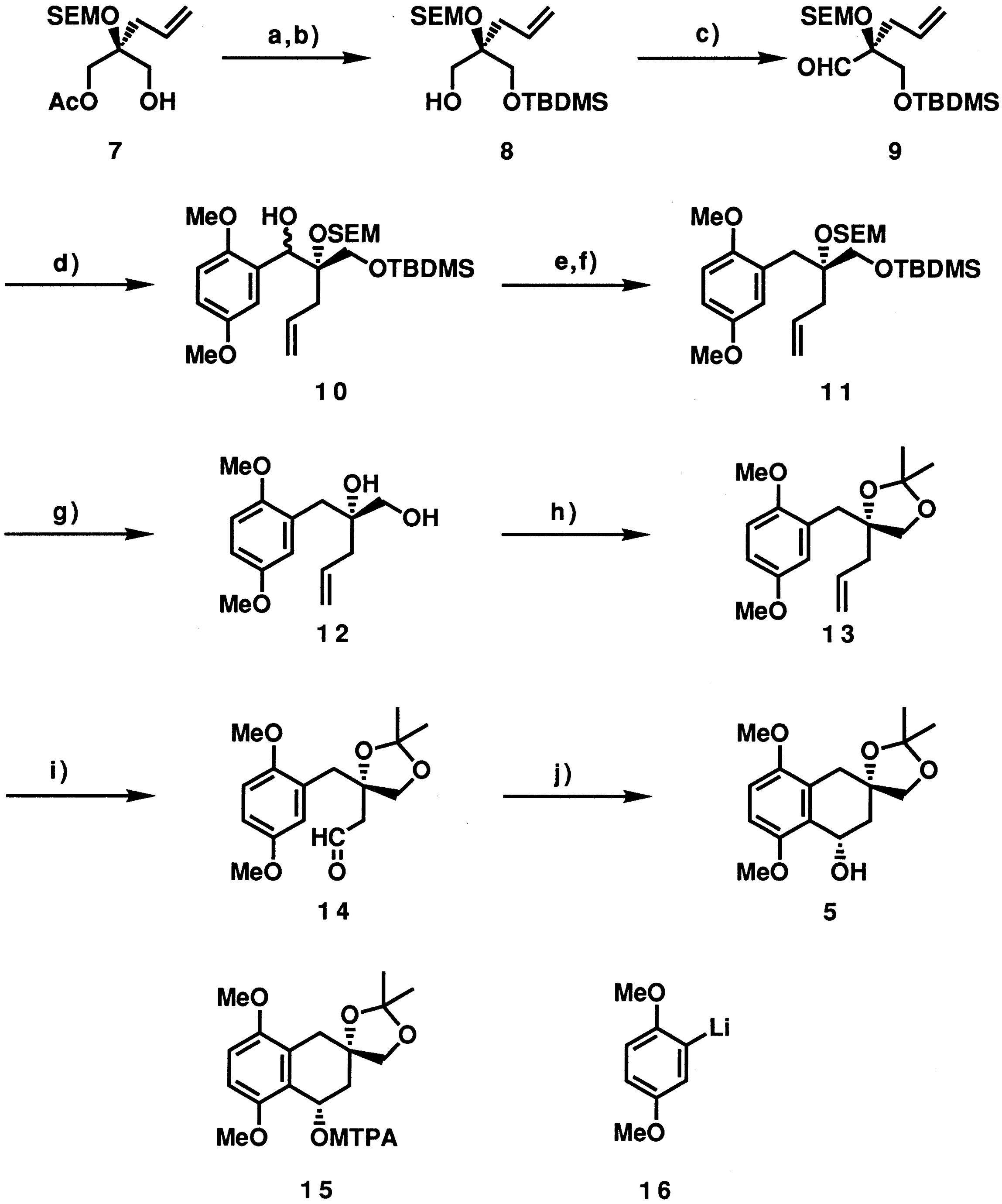
In the preceding paper,[4] we have demonstrated that enzymatic hydrolysis of prochiral diacetate **6** using lipase LP afforded optically active monoacetate **7** of 87%e.e. in good yield. This monoacetate was planned to be applied in the asymmetric synthesis of (+)-(1*S*,3*S*)-1,3-dihydroxy-3,3'-O-isopropyridene-3-(hydroxymehyl)-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (**5**), [5] which is one of versatile synthetic intermediates of anthracycline antibiotics.



Scheme 1.

In our synthesis illustrated in Scheme 2, the key intermediate is acetonide **13**[5] on the basis of Monneret's synthesis. First, to construct the correct configuration of asymmetric carbon at C-3 of **5**, monoacetate **7** was converted to its "enantiomeric" equivalent **8** by the treatment with t-butyldimethylsilyl (TBDMS) chloride, and subsequent removal of acetyl group with K_2CO_3/MeOH (93%/2steps). Oxidation of alcohol **8** with pyridinium dichromate gave aldehyde **9** in 90% yield. Coupling of aldehyde **9** with 2,5-dimethoxyphenyllithium (**16**) at –78 °C resulted the adduct **10** in 88% yield. Deoxygenation of **10** according to Barton's procedure[6] led to **11** in 82% yield. Deprotection of both hydroxy group in **11** using tetrabutylammonium fluoride[7] gave **12** in 86% yield, which in turn was protected as acetonide to afford the key intermediate **13**[5] in 86% yield. The next task was the preparation of aldehyde from olefin moiety. Ozonolysis of **13** followed by usual reductive workup gave only a disappointing yield [49%; 50% in lit.[5]] of **14**, accompanied by 21% yield of surprisingly stable ozonide which withstood to most of reductive reagents. We then turned our attention to the catalytic osmium tetroxide oxidation,[8] which provided aldehyde **14** in an improved yield (69%).

Ring closure of **14** by the aid of tin (IV) chloride afforded desired (1*S*,3*S*)-**5** in good yield (80%). The configuration of **5** was unambiguously established by nuclear Overhauser effect [10.2% between H-1 and H-2 (ax), 5.4% between H-1 and H-2 (eq)]. Its e.e. was confirmed to be 85% by HPLC analysis (DuPont, Zorbax SiO_2) of the corresponding MTPA ester **15**,[9] which was in good accordance with that of starting material. Although the recystallization of **5** from a mixture of hexane and acetone had no effect in enhancing the e.e. of **5**, the appropriate solvent (hexane/dichloromethane) dramatically changed the situation to give almost enantiomerically pure **5**[10] (98%e.e., 61% yield).



a) TBDMSCl, imidazole/DMF; b) K_2CO_3/MeOH; c) PDC, MS3A/CH_2Cl_2;
d) **16**/THF -78 °C; e) NaH, CS_2, MeI/THF; f) n-Bu_3SnH, AIBN/toluene;
g) TBAF, MS4A/DMPU; h) 2,2-dimethoxypropane, p-TsOH/acetone;
i) cat OsO_4, $NaIO_4$/dioxane-water(1:1); j) $SnCl_4$/CH_2Cl_2 -78 °C

Scheme 2.

In conclusion, an important key intermediate **5** for anthracycline antibiotics synthesis was prepared from **7** in 10 steps with 25% overall yield.

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10) $[\alpha]_D^{23}$ +32.8° (c 0.50, $CHCl_3$); lit.[5] +31° (c 0.73, $CHCl_3$).

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