

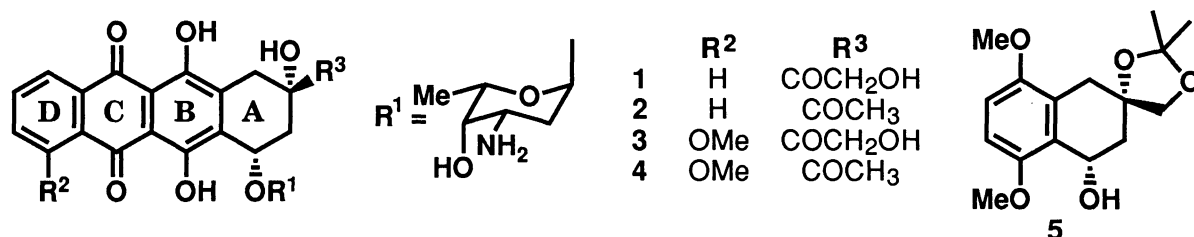
An Approach to Anthracycline Synthetic Intermediate from Novel Glycerol-related Chiral Pool[†]

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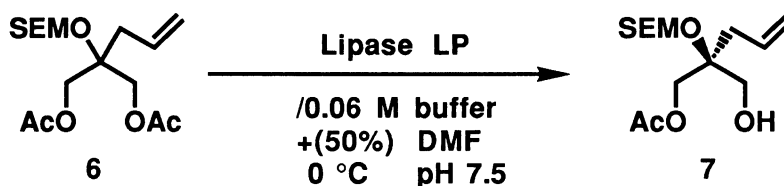
A key-intermediate of synthetic anthracycline, (+)-(1*S*,2*S*)-1,3-dihydroxy-3'-*O*-isopropiridene-3-(hydroxymethyl)-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene was synthesized from optically active 2-substituted glycerol monoacetate which was prepared via enantioselective enzymatic hydrolysis of a prochiral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



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

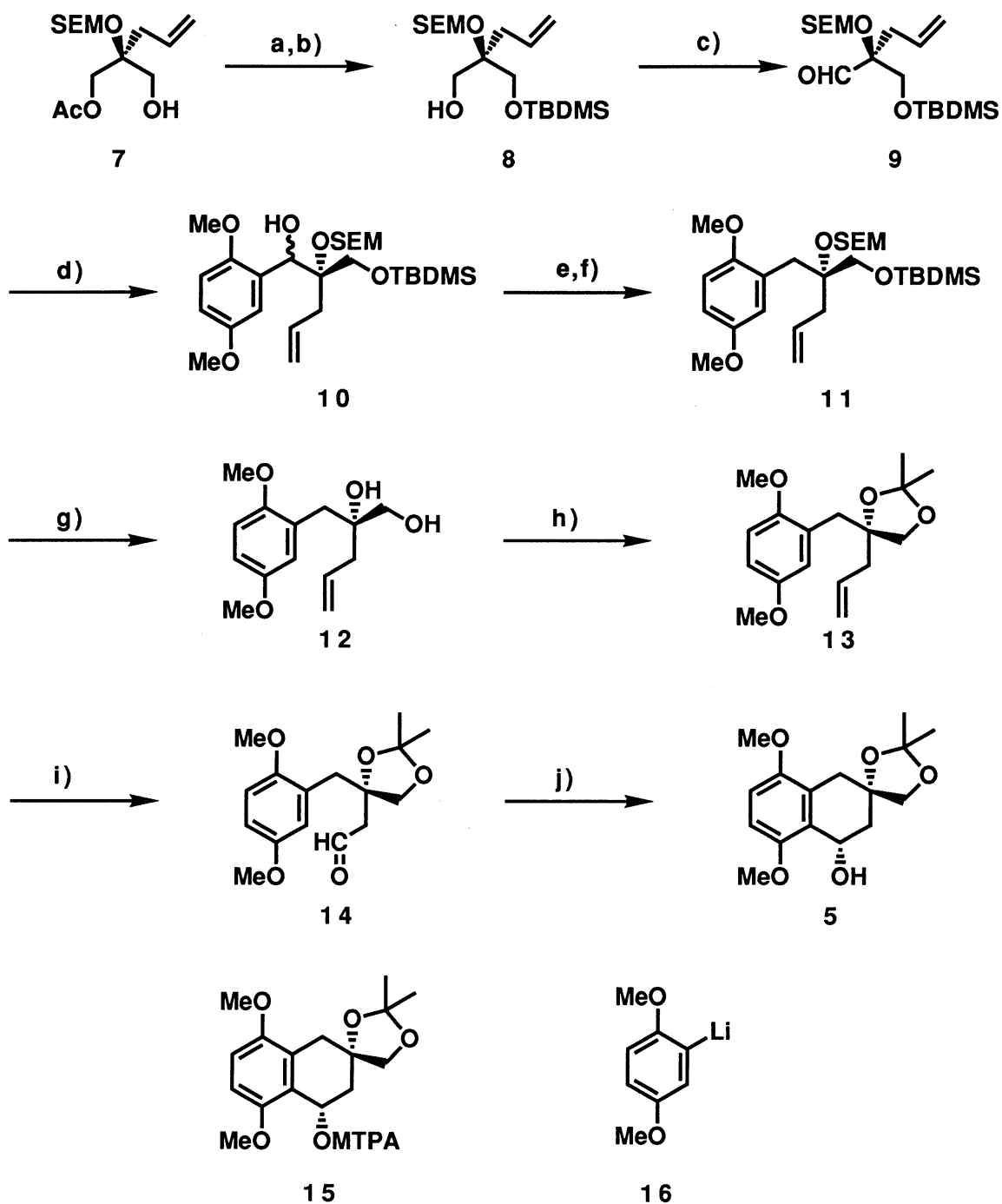
In the preceding paper,⁴⁾ we have demonstrated that enzymatic hydrolysis of prochiral diacetate **6** using lipase LP afforded optically active monoacetate **7** of 87%e.e. in good yield. This monoacetate was planned to be applied in the asymmetric synthesis of (+)-(1*S*,3*S*)-1,3-dihydroxy-3,3'-O-isopropylidene-3-(hydroxymethyl)-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (**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 $\text{K}_2\text{CO}_3/\text{MeOH}$ (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 procedure⁶⁾ led to **11** in 82% yield. Deprotection of both hydroxy group in **11** using tetrabutylammonium fluoride⁷⁾ 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 recrystallization 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) $\text{K}_2\text{CO}_3/\text{MeOH}$; c) PDC, MS3A/ CH_2Cl_2 ;
 d) **16**/THF -78°C ; e) NaH, CS_2 , MeI/THF; f) $n\text{-Bu}_3\text{SnH}$, AIBN/toluene;
 g) TBAF, MS4A/DMPU; h) 2,2-dimethoxypropane, $p\text{-TsOH}$ /acetone;
 i) cat OsO_4 , NaIO_4 /dioxane-water(1:1); j) $\text{SnCl}_4/\text{CH}_2\text{Cl}_2$ -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) $[\alpha]_D^{23} +32.8^\circ$ (c 0.50, CHCl_3); lit.⁵⁾ $+31^\circ$ (c 0.73, CHCl_3).

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