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# STEREOSPECIFIC SYNTHESIS OF *EXO*-ALLYLIC ALCOHOL. AN EFFICIENT ASYMMETRIC SYNTHESIS OF (*R*)-(-)-2-ACETYL-5,8-DIMETHOXY-1,2,3,4-TETRAHYDRO-2-NAPHTHOL[1]

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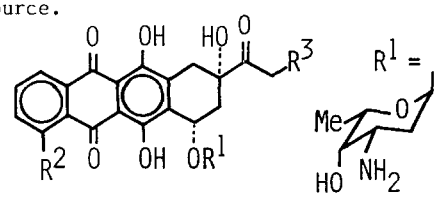
*Summary: A method for the stereospecific synthesis of exo-allylic alcohols with trisubstituents is described. Using this methodology in combination with Sharpless catalytic asymmetric epoxidation, an efficient synthesis of (R)-(-)-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (5), an important intermediate for the anthracycline synthesis, has been accomplished in 36% overall yield from 5,8-dimethoxy-2-tetralone (6) with 93% e.e..*

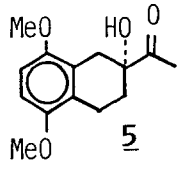
4-Demethoxyadriamycin (**1**) and 4-demethoxydaunorubicin (**2**) are expected to be more clinically useful antineoplastic agents than naturally occurring anthracyclines **3** and **4**.[2] Since these analogues are not available by fermentation method, a quite number of synthetic studies on **1** and **2** have been already reported, establishing that (*R*)-(-)-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (**5**) is one of the most useful synthetic intermediates.[3] Recently Terashima and his coworkers have reported an elegant and improved synthesis of (*R*)-(-)-**5** using the intramolecular bromolactonization as a key step.[4] We herein wish to report a completely different synthesis of (*R*)-(-)-**5**, which features a catalytic use of the chiral source.



$R^1$ =



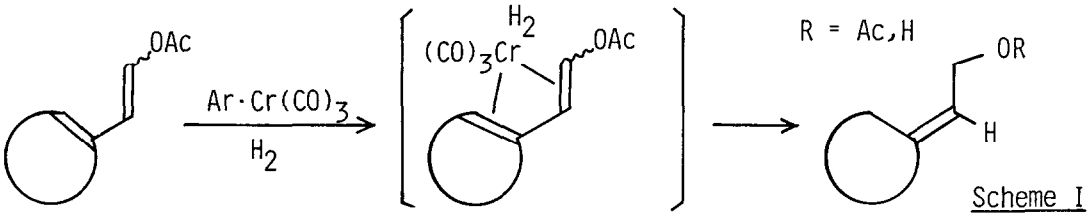
| | | | |
|---|---|---|---|
| $R^2$ = H , | $R^3$ = OH | **1** |
| $R^2$ = H , | $R^3$ = H | **2** |
| $R^2$ = OMe, | $R^3$ = OH | **3** |
| $R^2$ = OMe, | $R^3$ = H | **4** |



**5**

We undertook the synthesis of (*R*)-(-)-**5** using Sharpless asymmetric epoxidation.[5] Recently Sharpless and his coworkers have found the first general procedure for the asymmetric epoxidation of allylic alcohols using a catalytic amount of diethyl tartrate and titanium(IV) isopropoxide.[6] For the efficient use of this excellent reaction the olefin geometry of the allylic alcohol **12** has to be strictly controlled. However, unfortunately there was no methodology for the stereospecific synthesis of *exo*-allylic alcohols. Therefore, first of all we focused our attention on the development of an efficient method for the stereospecific synthesis of **12**.

We have recently exploited an extremely efficient method for the stereospecific synthesis of *exo*-tri- and tetrasubstituted olefins using the 1,4-hydrogenation of conjugated dienes catalyzed by arene·$Cr(CO)_3$ complexes.[7] This successful result led us to expect that extension of the 1,4-hydrogenation technique to dienol acetates could produce *exo*-allylic alcohols stereospecifically (Scheme I). Thus, the efficient synthesis of the requisite dienol acetate **10** was first investigated in order to examine the 1,4-hydrogenation reaction.




Scheme I

The synthesis of **10** started with the allyl-alcohol **7**, which was obtained efficiently from highly enolizable **6** according to the reported procedure.[8,9] Treatment of **7** with a catalytic amount of osmium tetroxide and 3 eq of sodium periodate in aqueous ether (ether-$H_2O$, 3:4) at room temperature afforded the rather unstable aldehyde **9**,[10] which, without purification, was converted to the dienol acetate **10**[11] regio- and stereospecifically[12] on exposure to 5 eq of acetic anhydride, 8 eq of triethylamine and a catalytic amount of 4-dimethylaminopyridine in toluene at 80 °C for 40 min (60% overall yield from **7**). The better overall yield was obtained by the following sequence. Acetylation of **7** (5 eq of $Ac_2O$, 5 eq of pyridine and cat. DMAP in $CH_2Cl_2$) gave the acetate **8**,[11] which was transformed into the dienol acetate **10** regio- and stereospecifically on exposure to the same reaction conditions as described above in 73% overall yield.

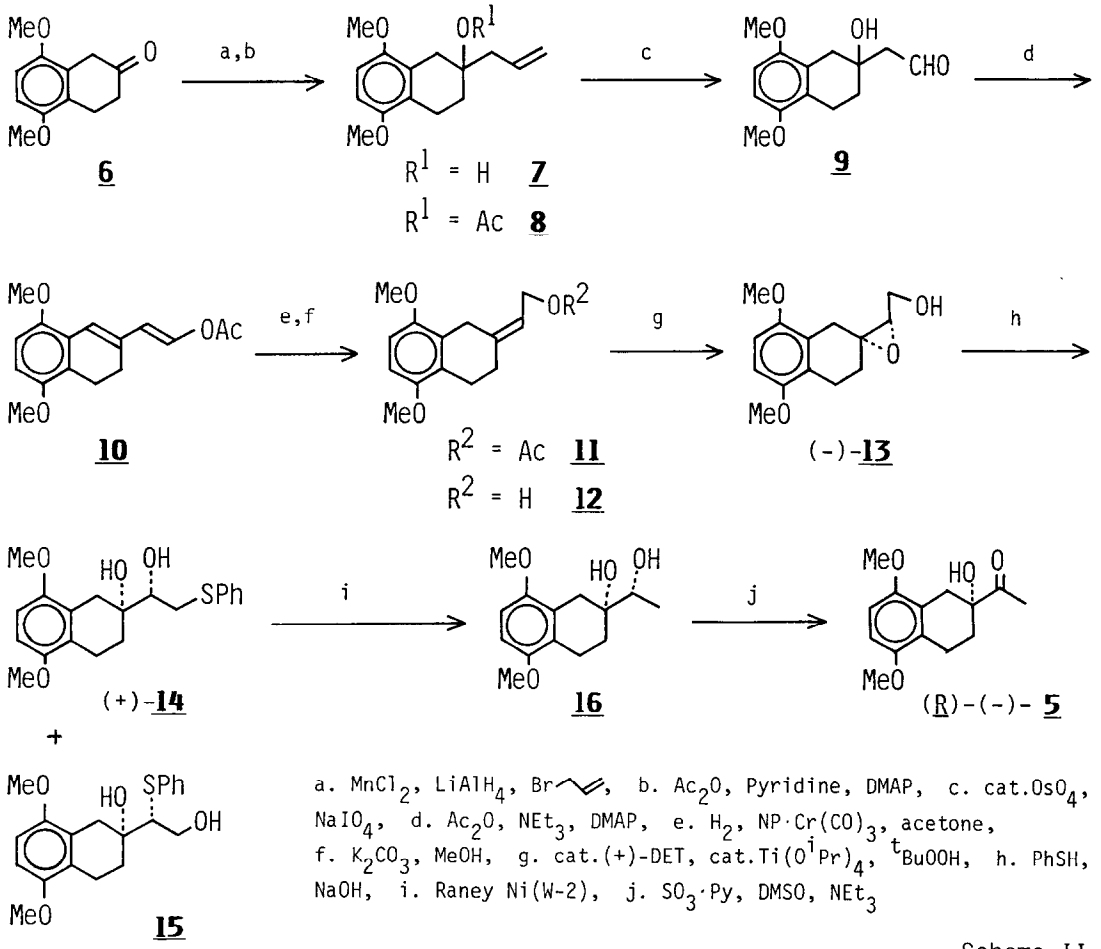
As expected the crucial 1,4-hydrogenation of the dienol acetate **10** proceeded smoothly by using naphthalene·$Cr(CO)_3$[13] as a catalyst to afford the stereochemically homogeneous *Z*-allylic acetate **11**[14,15,16] in 91% yield (20 mol% of the catalyst, acetone solvent, 140 kg/cm$^2$ of $H_2$ pressure, 45 °C, 13 hr) together with recovery of **10** (9%). The obtained allylic acetate **11** was then converted to the allylic alcohol **12**[11] in quantitative yield on exposure to potassium carbonate in methanol.

With the efficient and stereospecific synthesis of the *exo*-allylic alcohol **12** in hand, next we turned our attention to the transformation of **12** into (*R*)-(-)-**5**. Sharpless asymmetric epoxidation of **12** proceeded smoothly (15 mol% of (+)-diethyl tartrate, 10 mol% of titanium-(IV) isopropoxide, 2 eq of *t*-butylhydroperoxide, molecular sieves 4A, -40 °C, 2.5 hr),[6] providing the optically active and crystalline epoxy-alcohol **13**[11] in 97% yield. An enantiomeric excess of 93% was determined by $^1H$ NMR analysis (400 MHz) of the corresponding MTPA ester[17] of **13**. Recrystallization of this sample from $CH_2Cl_2$-*n*-hexane gave optically pure (-)-**13**[18] ($[\alpha]_D^{20}$ -21.7 °(*c* 0.725, $CHCl_3$), mp 145-146 °C). Treatment of optically pure **13** with thiophenol under the basic conditions (slow dropping of PhSH to a solution of **13** in 0.5 *N* NaOH aq-*t*-BuOH (3:2) at 85-90 °C)[19] afforded the desired dihydroxy-sulfide **14**[11] via Payne rearrangement in 76% yield[20] (colorless fine needle from $CHCl_3$-*n*-hexane, mp 135-136 °C, $[\alpha]_D^{20}$ +23.9 °(*c* 0.750, $CHCl_3$)) together with a small amount of the isomer **15** (17%). Hydrogenolysis of the carbon-sulfur bond of **14** was carried out with Raney Ni (W-2) in boiling ethanol,

giving the diol **16**[14] in 90% yield ($[\alpha]_D^{20}$ -43.2 °(*c* 0.905, EtOH)). Finally the diol **16** was converted to (*R*)-(-)-**5** in 84% yield on exposure to 10 eq of sulfur trioxide pyridine complex and 30 eq triethylamine in DMSO at room temperature (colorless prism from ether–*n*-hexane, mp 128-129 °C, $[\alpha]_D^{20}$ -48.7 °(*c* 0.825, $CHCl_3$); lit.[3e] mp 128-129 °C, $[\alpha]_D^{20}$ -48.8 °(*c* 1, $CHCl_3$), lit.[4] mp 129.5-130 °C, $[\alpha]_D^{20}$ -47.6 °(*c* 1.02, $CHCl_3$), lit.[3b] mp 128-129 °C, $[\alpha]_D^{20}$ -48.2 °(*c* 0.982, $CHCl_3$))(Scheme II).

In summation, we have accomplished an asymmetric synthesis of (*R*)-(-)-**5**, a well-known intermediate for the synthesis of anthracyclines,[3] in 36% overall yield starting with **6**. The synthesis presented above involves a new and efficient method for the stereospecific synthesis of *exo*-allylic alcohols and a catalytic asymmetric induction process.

Acknowledgement: We are grateful to Dr. Shiro Terashima for many helpful discussions. Thanks are also given to Professor K.B. Sharpless for providing a preprint of his most recent paper on Sharpless catalytic asymmetric epoxidation.




a. $MnCl_2$, $LiAlH_4$, Br⟋⟍, b. $Ac_2O$, Pyridine, DMAP, c. cat.$OsO_4$, $NaIO_4$, d. $Ac_2O$, $NEt_3$, DMAP, e. $H_2$, NP·$Cr(CO)_3$, acetone, f. $K_2CO_3$, MeOH, g. cat.(+)-DET, cat.$Ti(O^iPr)_4$, $^tBuOOH$, h. PhSH, NaOH, i. Raney Ni(W-2), j. $SO_3$·Py, DMSO, $NEt_3$

Scheme II

## References and Notes


1) This paper is dedicated to Professor Shun-ichi Yamada on the occasion of his 70th birthday.

2) S. Neidel, *Nature* (London), 268, 195 (1977).

3) a. S. Terashima, *Yuki Gosei Kagaku Kyokai Shi*, 40, 20 (1982); b. S.-s. Jaw, S. Terashima, and K. Koga, *Chem. Pharm. Bull.*, 27, 2351 (1979); c. N. Tanno and S. Terashima, *ibid.*, 31, 811, 821, (1983); d. K. Tamoto and S. Terashima, *ibid.*, 32, 4328 (1984); e. A.V.R. Rao, J.S. Yadav, K.B. Reddy, and A.R. Mehendale, *J. Chem. Soc. Chem. Commun.*, 453 (1984); f. K. Tamoto, M. Sugimori, and S. Terashima, *Tetrahedron*, 40, 4617 (1984); g. R.A. Russell, A.S. Krauss, S. Adrian, R.W. Irvine, and R.N. Warrener, *Aust. J. Chem.*, 38, 179 (1985).

4) M. Suzuki, Y. Kimura, and S. Terashima, *Chemistry Lett.*, 367 (1985).

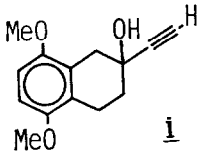
5) T. Katsuki and K.B. Sharpless, *J. Am. Chem. Soc.*, 102, 5976 (1980).

6) Personal communication from Professor K.B. Sharpless.

7) a. M. Shibasaki, M. Sodeoka, and Y. Ogawa, *J. Org. Chem.*, 49, 4096 (1984); b. M. Shibasaki and M. Sodeoka, *Tetrahedron Lett.*, 26, 3491 (1985); c. M. Shibasaki and M. Sodeoka, *Yuki Gosei Kagaku Kyokai Shi*, 43, 877 (1985).

8) T. Hiyama, M. Sawahata, and Y. Kusano, *Chemistry Lett.*, 611 (1985).

9) Another route utilizing ethynyl-alcohol **i** was found to be unsuccessful. The dienol acetate **10** was obtained only in a low overall yield from **i**.



**i**

10) The separated organic layer was filtrated through a pad of $Na_2SO_3$-$Na_2SO_4$-$SiO_2$. The filtrate was then evaporated in vacuo to give crude **9**.

11) Satisfactory data (elemental analysis, $^1H$ NMR, IR and Mass) were obtained for each synthetic intermediate.

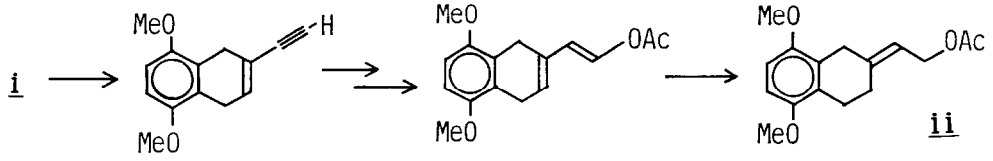
12) Both the *E*-dienol acetate and the *Z*-dienol acetate should afford the 1,4-hydrogenation product **11** in good yields respectively because of no possibility of 1,5-hydrogen shift under the hydrogenation conditions. However, 1,4-hydrogenation of the *E*-dienol acetate should proceed under the milder conditions than that of the *Z*-dienol acetate.

13) a. S. Top and G. Jaouen, *J. Organomet. Chem.*, 182, 381 (1979); b. E.O. Fischer, K. Öfele, H. Essler, W. Fröhlich, J.P. Mortensen, and W. Semmlinger, *Chem. Ber.*, 91, 2763 (1958).

14) Satisfactory data ($^1H$ NMR, IR, Mass and exact Mass) were obtained for each synthetic intermediate.

15) A part of **11** (4%) was isolated as its chromium complex, which was easily converted to **11** on exposure to $FeCl_3$/EtOH.

16) The stereochemistry of **11** was strongly assumed to be *Z* based on the mechanistic ground of the 1,4-hydrogenation and supported by the result of Sharpless asymmetric epoxidation of **12**. Furthermore, comparison of $^1H$ NMR spectra (**11** and **ii**) showed clearly that the 1,4-hydrogenation product was stereochemically homogeneous. The stereoisomer **ii** was synthesized as shown below.




17) J.A. Dale, D.L. Dull, and H.S. Mosher, *J. Org. Chem.*, 34, 2543 (1969).

18) >97% e.e. from 400 MHz $^1H$ NMR spectrum of its MTPA ester.

19) C.H. Behrens and K.B. Sharpless, *Aldrichimica Acta*, 16, 67 (1983).

20) Direct reduction of **13** with $NaBH_4$ under the basic conditions gave **16** only in 36% yield.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