An Enantioselective Synthesis of Anthracycline Precursors

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Summary: A highly enantioselective synthesis of anthracycline precursors (**1a** and **10**) was accomplished through a chirality-transfer ene reaction.

Because of their significant biological activity, anthracycline antibiotics[1] (e.g., adriamycin and daunomycin) have been important targets in synthetic organic chemistry. We describe herein an efficient synthetic method for preparation of optically pure precursors of these antibiotics.[2] In a previous paper, we reported a chirality-transfer ene reaction between (*S*)-3-(*tert*-butyldimethylsiloxy)-2-(ethylthio)-1-butene with aldehydes,[3] giving highly enantiomerically pure ene adducts in reactions with aromatic aldehydes. On the basis of these results, we have extended this methodology for the synthesis of the optically pure anthracycline substrates **1a** and **1b** (Figure 1).

We chose 5-methoxy-2-(triisopropylsiloxy)benzaldehyde, which was easily prepared from commercially available 2-hydroxy-5-methoxybenzaldehyde, as an enophile. Under the influence of Me_2AlCl, the reaction of aldehyde **2** with (*S*)-3-(*tert*-butyldimethylsiloxy)-2-(methylthio)-1-butene afforded nearly enantiomerically pure (99% ee)[4] ene adduct **3** in 95% yield.

The neighboring effects of both hydroxy and methoxy groups enabled regioselective lithiation[5] at the 6-position of **3** using butyllithium[6] in hexane. Subsequent treatment of the lithiated species with paraformaldehyde afforded the hydroxymethylation product **4** in 78% yield (ca. 90% yield based on unrecovered starting material).

It was necessary to next convert the primary alcohol moiety of **4** into a good leaving group to allow ring closure under mild enough reaction conditions so as not to aromatize the A ring.[7] Treatment of **4** with $Ph_3P/(CCl_3)_2CO$/2,6-lutidine[8] at low temperature formed the desired primary benzyl chloride selectively, which was too unstable for subsequent manipulation.

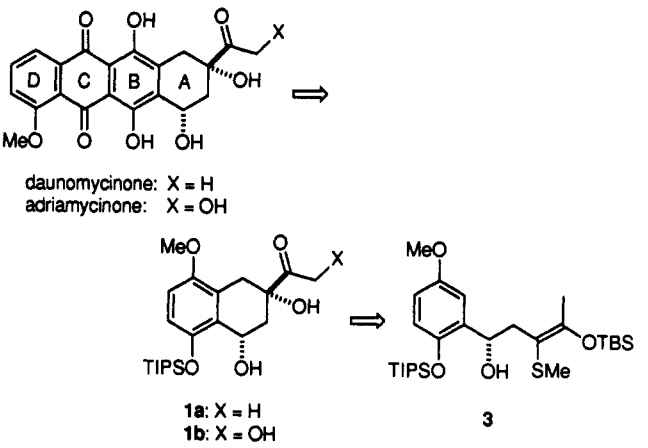


Figure 1.

The trichloroacetate **5**, selectively prepared by the reaction of **4** with hexachloroacetone[9] and ethyldimethylamine in CH_3CN–CH_2Cl_2, proved to be an excellent leaving group. Even with weak Lewis acids such as Me_2AlCl, **5** underwent ring closure cleanly at −78 °C to give the bicyclic ketone **6** in 62% overall yield as a single stereoisomer[10] whose stereochemistry was assigned as 7*S*,9*S*[11] by X-ray crystallographic analysis.[12]

The hydroxy group of **6** was protected as the acetate, and the α-alkylthio keto group of **7** was converted to the enol silyl ether **8** by heating with activated zinc[13] and chlorotriethylsilane. Under these conditions a fair amount of hydrolyzed ketone was also formed. However, in the presence of diethylzinc, the desired enol silyl ether was obtained in high yield. After removal of the acetyl group with DIBAL, enol silyl ether **9** was treated with *tert*-butyl hydroperoxide in the presence of $VO(acac)_2$[14] in toluene to afford the *cis* diol **1a** in 69% yield.[15]

Interestingly, the oxidation of **9** in CH_2Cl_2 gave the diol **10** containing the α,α′-dihydroxyacetone side chain via a double hydroxylation reaction.[16]

(1) (a) Lown, J. W., Ed. *Anthracycline and Anthracenedione-Based Anticancer Agents*; Elsevier: Amsterdam, 1988. (b) Arcamone, F. *Med. Res. Rev.* **1984**, *4*, 153.

(2) Enantioselective synthesis of anthracyclinones: (a) Krohn, K.; Ekkundi, V. S. In *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier: Amsterdam, 1989; Vol. 4, pp 317–366. (b) Krohn, K. In *Progress in the Chemistry of Natural Products*; Herz, W., Griesbach, H., Kirby, G. W., Tamm, Ch., Eds.; Springer-Verlag: Wien, New York, 1989; Vol. 55, p 1. (c) Watanabe, N.; Ohta, H. *Chem. Lett.* **1992**, 661 and references cited therein.

(3) Tanino, K.; Shoda, H.; Nakamura, T.; Kuwajima, I. *Tetrahedron Lett.* **1992**, *33*, 1337.

(4) Ozonolysis of the adduct **3** followed by oxidation with *m*-CPBA in absolute ethanol afforded ethyl 3-hydroxy-3-[5-methoxy-2-(triisopropylsiloxy)phenyl]propionate. The enantiomeric excess of **3** was determined in HPLC analysis of the (*R*)-MTPA ester of the β-hydroxy ester.

(5) (a) House, H. O.; Bare, T. M.; Hanners, W. E. *J. Org. Chem.* **1969**, *34*, 2209. (b) Uemura, M.; Tokuyama, S.; Sakan, T. *Chem. Lett.* **1975**, 1195.

(6) Use of stronger bases such as *sec*-butyllithium or *tert*-butyllithium led to decreased regioselectivity.

(7) Use of stronger Lewis acids facilitated aromatization of the A ring, probably through dehydration and subsequent loss of methanethiol.

(8) Magid, R. M.; Fruchey, O. S.; Johnson, W. L.; Allen, T. G. *J. Org. Chem.* **1979**, *44*, 359.

(9) (a) Simmons, H. E.; Wiley, D. W. *J. Am. Chem. Soc.* **1960**, *82*, 2288. (b) Panetta, C. A.; Casanova, T. G. *J. Org. Chem.* **1970**, *35*, 2423.

(10) The hydroxy group might react with Me_2AlCl to form an aluminum alkoxide. The diastereoselective formation of **6** may be accounted for by coordination of the Al to the siloxy oxygen in the transition-state structure.

(11) The numbering is based on that of the anthracyclinones.

(12) Treatment of **6** with TBAF followed by benzoylation afforded the corresponding dibenzoate as colorless crystals. X-ray crystallographic analysis of the dibenzoate gave the absolute configuration: Kamei, S.; Sakai, Y.; Ohashi, Y.; Adachi, A.; Tanino, K.; Kuwajima, I. *Acta Crystallogr., Section C*, in press.

(13) Rieke, R. D.; Li, P. T.-J.; Burns, T. P.; Uhm, S. T. *J. Org. Chem.* **1981**, *46*, 4323.

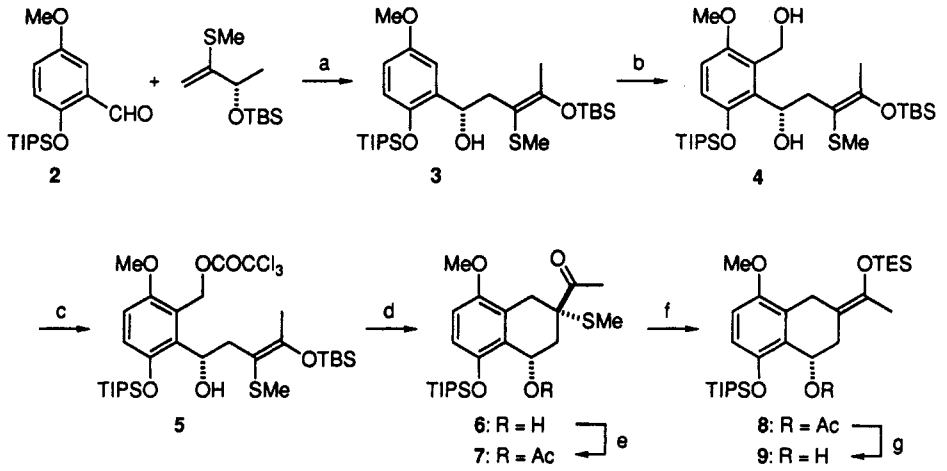
(14) Hauser, F. M.; Hewawasam, P. *J. Org. Chem.* **1988**, *53*, 4515.

(15) The diols **1a** and **10** were treated with phenyl boronic acid and a catalytic amount of *p*-toluenesulfonic acid to afford the corresponding cyclic boronates indicating that both of these diols are *cis* isomers.

(16) (a) Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 6257. (b) Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 3324.

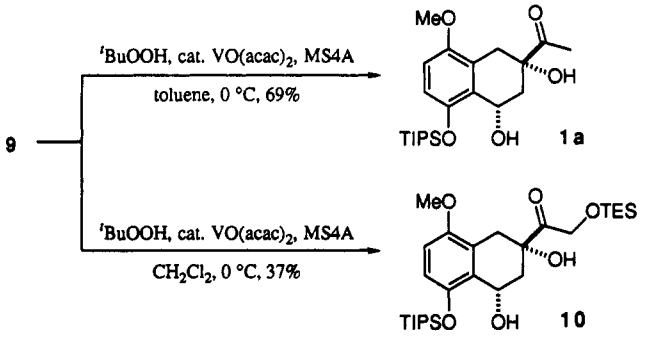
0022-3263/93/1958-4189$04.00/0

Scheme I[a]



[a] Key: (a) Me_2AlCl, toluene, −78 °C, 95% (99% ee); (b) BuLi, hexane, 0 °C, then $(CH_2O)_n$, rt, 78%; (c) $(CCl_3)_2CO$, Me_2NEt, CH_3CN–CH_2Cl_2, 0 °C; (d) Me_2AlCl, CH_2Cl_2, −78 °C, 62% from 4; (e) Ac_2O, Py, DMAP, rt, 97%; (f) Zn, TESCl, Et_2Zn, THF, reflux, 86%; (g) DIBAL, CH_2Cl_2, −78 °C, 99%.

Scheme II



Since conversion of compounds analogous to **1a** or **10** into natural anthracyclinones has been reported by several groups,[17] **1a** and **10** can be easily converted to daunomycinone and adriamycinone, respectively.

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Supplementary Material Available: Experimental procedures and spectral data for **1**–**10** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(17) (a) Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. *J. Chem. Soc., Chem. Commun.* **1982**, 158. (b) Irvine, R. W.; Kinloch, S. A.; McCormick, A. S.; Russell, R. A.; Warrener, R. N. *Tetrahedron* **1988**, *44*, 4591. (c) Hauser, F. M.; Hawawasam, P.; Rho, Y. S. *J. Org. Chem.* **1989**, *54*, 5110. (d) Hauser, F. M.; Tommasi, R. A. *J. Org. Chem.* **1991**, *56*, 5758.