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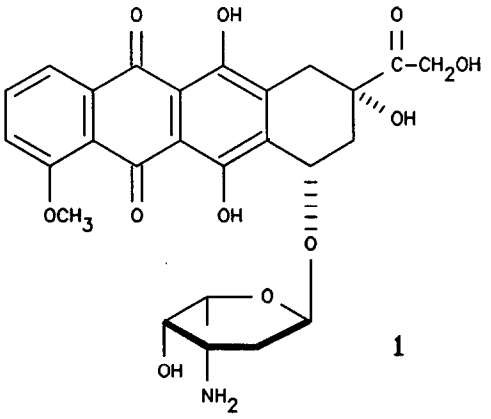
SYNTHESIS OF A RING A PRECURSOR OF DOXORUBICIN: STEREOSELECTIVE CONTROL OF THE EPOXIDATION OF A HOMOALLYLIC ALCOHOL BY HYDROXYL AND ESTER GROUPS

Timothy Chamberlain, Xiaoping Fu, James T. Pechacek, Xin Peng, Desmond M. S. Wheeler* and Margaret M. Wheeler.

Department of Chemistry, University of Nebraska, Lincoln, NE 68588-0304 USA

Abstract: The key step in a synthesis of a precursor for ring A in doxorubicin is the stereoselective control of the epoxidation of a homoallylic alcohol by ester and hydroxyl groups; the result leads to a new method of forming lactones in excellent yields under neutral conditions.

Many syntheses of the important anticancer drug doxorubicin **1** and related compounds have been reported.[1] Comparatively few are stereoselective and of these only three[2] involved introducing the *cis* C_7,C_9 diol before the tetracyclic skeleton had been completed.[3]



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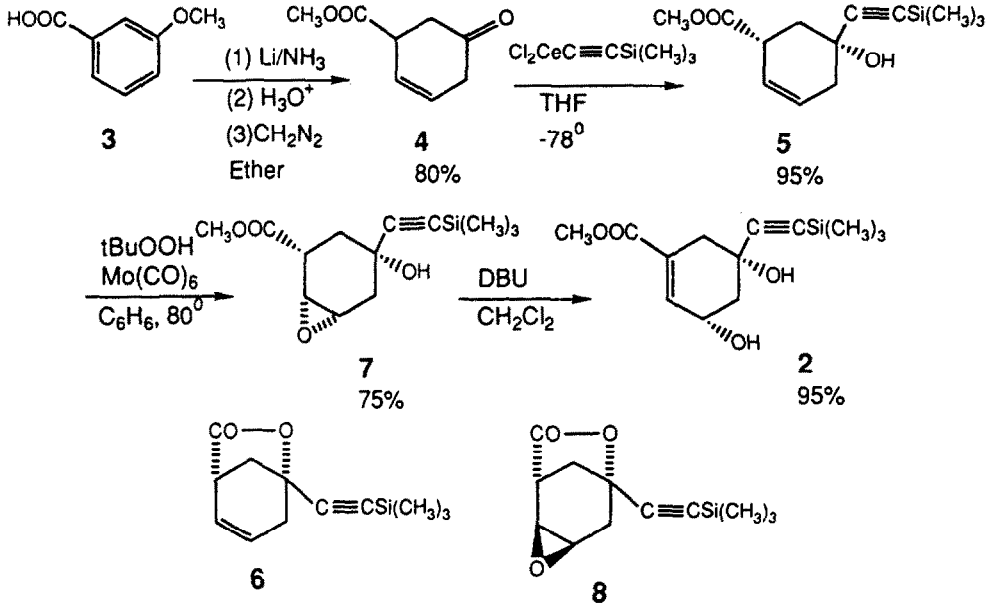
We now report a stereoselective synthesis in 5 steps of the diol **2**[4], a precursor for the A ring, in 54% overall yield from *m*-anisic acid, **3** (Scheme 1). The key step **5** → **7** is a stereoselective epoxidation controlled

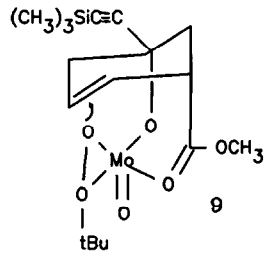
by a homoallylic alcohol and an ester group. The addition of dichloroceriumtrimethylsilylacetylide[5] to the keto ester 4[6] at -78°C gave the adduct 5[4]. The stereochemistry of 5[8], was established by the fact that when the reaction was allowed to come to room temperature before being quenched, the lactone 6[4] was isolated.

Epoxidation of 5 by *t*-butyl hydroperoxide in refluxing benzene in the presence of molybdenum hexacarbonyl[9] yielded the epoxide 7[4,10] (75%). The structure of 7 was confirmed by the fact that the diol 2[11] obtained from 7 was converted into an acetonide and a carbonate. Two byproducts[12], the lactone 6[4] and the epoxy lactone 8[4], and starting material (5 - 10%) were also isolated from the epoxidation.

Scheme I



Pearson[13] has shown that an ester group has a *cis* directing effect on epoxidations using *t*-butyl hydroperoxide catalyzed by molybdenum hexacarbonyl. This led us to suspect that the epoxidation of 5 to 7 might involve an intermediate of the type 9. The idea is supported by the fact that 5 and 7 are converted in excellent yields into the lactones 6 and 10[14] respectively when refluxed in benzene in the presence of molybdenyl acetylacetonate.[15] Little lactone was formed in the absence of the catalyst. This method provides a way of making lactones under neutral conditions[16]. Although the *cis* directing effect of allylic and homoallylic hydroxyls in epoxidations is used frequently in syntheses[9], *we know of no previous explicit claim of epoxidation being directed by 2 groups.*[17]



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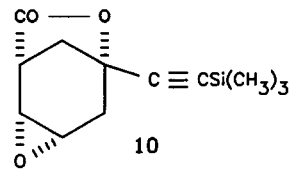

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10. Spectral data for **7**: IR(KBr): ν_{max} 3360 (OH), 2160 (C≡C), 1732 (C=O), 1260, 845 cm^{-1}; ^1H NMR

($CDCl_3$): δ 3.8 (s, 3H, $COOCH_3$), 3.5 (q, 1H, CH_2CHO), 3.3 (d, 1H, $CHOCHCH_2$), 3.25 (m, 1H, CHCOO) 2.4 (dd, 1H, CH_2), 2.3 (s, 1H, OH), 2.0 (d, 1H, CH_2), 1.85 (m, 2H, CH_2), 0.17 (s, 9H, $C{\equiv}CSi(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 172.45 (COO), 107.43 ($SiC{\equiv}C$), 89.47 ($C{\equiv}C$), 66.26, 52.2, 51.80, 50.71, 40.92, 38.26, 31.03, 0.20 ($Si(CH_3)_3$).

11. Spectral data for **2**: IR (CH_2Cl_2): ν_{max} 3310 (OH), 2158 ($C{\equiv}C$), 1721 ($COOCH_3$), 1653 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.1 (s, 1H, $C{\equiv}CH$), 4.4 (m, all couplings less than 2 Hz, 1H, $CC\underline{H}(OH)$), 3.8 (s, 3H, $COOCH_3$), 3.0-3.4 (m, 1H, OH), 2.9-2.8 (dd, 2H, CH_2), 2.6 (s, 1H, OH), 2.5-2.2 (dd, 2H, CH_2), 0.17 (s, 9H, $C\text{-}CSi(CH_3)_3$); ^{13}C NMR ($CDCl_3$): 167.20 (C=O), 138.88, 127.60, 108.0, 88.52, 66.04, 61.62, 51.92, 41.74, 38.87, 0.228.
12. The combined yields of **6** and **8** amount to about 15%, though the relative amounts varied.
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14. Spectral (IR and ^1H NMR) and analytical data correspond to the structure shown.
15. The substrates **5** and **7** were refluxed in benzene for 3 h in the presence of $MoO_2(acac)_2$(0.1 equivalent) to give the lactones **6** and **8** respectively in yields exceeding 80%. Repitition of the experiments in the absence of the catalyst gave traces of the lactones.
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17. Warrener and coworkers [2c] describes a V^{+5} catalyzed stereoselective epoxidation of a dihydroxy compound in which one hydroxyl is allylic and the other homoallylic. We believe that their results can be best explained by a dicomplexing of both hydroxyls with the catalyst.

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