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A NEW SYNTHETIC ROUTE TO 4-DEMETHOXYDAUNOMYCINONE

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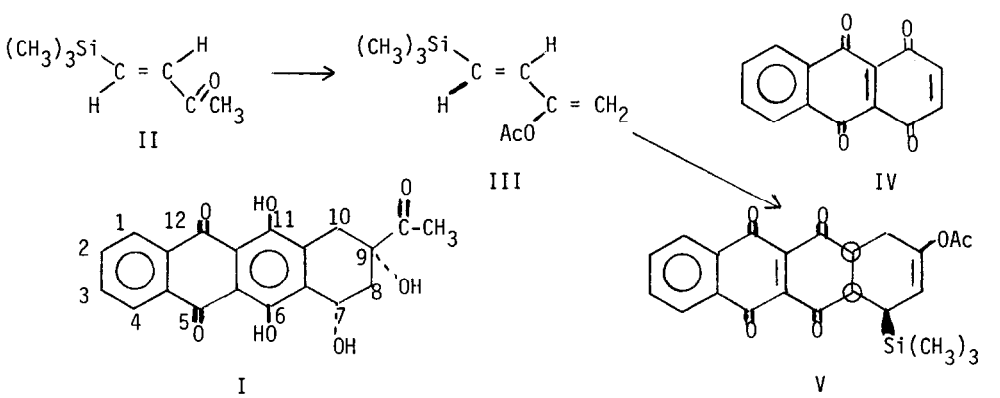
The clinical efficacy of the antitumor agents adriamycin and daunorubicin has stimulated numerous synthetic schemes toward the aglycones and variations therof.[1] By means of total synthesis 4-demethoxydaunomycin has been prepared from 4-demethoxydaunomycinone and found to be a potent antitumor agent.[2]

Many syntheses of the daunomycinone system involve a difficult benzylic bromination of the 7 position followed by solvolysis of the halogen to the corresponding hydroxyl[1a,b]. This approach tends to give poor yields of the desired product and does not always succeed. We wish to report a stereoselective synthesis of (±)-4-demethoxydaunomycinone (I)[3] that circumvents this problem. The reaction of aryl trimethylsilanes with lead tetrakistrifluoroacetate to form the corresponding aryl trifluoroacetates has been described.[4] We found that benzyltrimethylsilane underwent conversion to benzyl trifluoroacetate under similar conditions. It is significant to note that neither of these reactions occurred with lead tetraacetate in acetic acid even at reflux. On the basis of this discovery we planned a synthetic scheme where a 7-trimethylsilyl group would be used as a latent hydroxyl function.[5]

The reaction of trans-4-(trimethylsilyl)-3-buten-2-one (II)[6,7] with isopropenyl acetate and p-toluenesulfonic acid (20 hours controlled distillation to remove acetone) produced trans-4-(trimethylsilyl)-2-acetoxy-1,3-butadiene (III), (bp 45-47° / 0.1 mm) in 68% yield. Diels-Alder addition of this product to quinizarinquinone (IV)[8], (4 days, 50°, benzene) gave a 77% yield of adduct V, which on careful hydrolysis with sodium hydroxide led to the trione VI. Attempts at ethynylation of VI at C-9 under a variety of conditions gave only traces of product presumably due to the formation of the enolate stabilized by conjugation with the aromatic ring B.



Fortunately this serious difficulty was overcome by the simple process of converting the Diels-Alder adduct to the corresponding dihydro derivatives[1e]. Thus, catalytic hydrogenation ($Pd/BaSO_4$, THF) of V gave VII, mp 217-225° dec., in 94% yield. Upon refluxing in methanol with a small amount of concentrated hydrochloric acid a 93% yield of the dimethyl ketal VIII, mp 210-211°, was obtained. Hydrolysis to IX, mp 204-207°, was completed in virtually quantitative yield by solution in trifluoroacetic acid and slow addition of water[9]. In contrast to the results obtained with VI the trione IX reacted selectively at C_9 with ethynyl magnesium bromide in THF at 0° to yield X, 86%, mp 206-208° from methylene chloride-cyclohexane, and XI, 11%, mp 229-231° from benzene-cyclohexane[10]. Acetylation of X with isopropenyl acetate and p-toluenesulfonic acid (16 hours, 25°C) gave XII, mp 213-214°, in 95% yield.

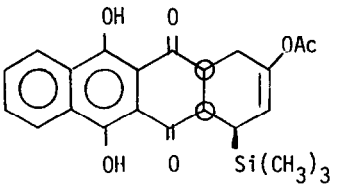
Reconversion to the anthraquinone system was achieved by oxidation of XII with lead tetraacetate in acetic acid to give the quinone XIII[11], which was isomerized to XV, mp 204-206°, by heating with potassium acetate in acetic acid (90°, 3 hours, 87%). In order to study the action of lead tetraacetate on the benzylic trimethylsilyl grouping in XV, it was necessary to prevent the oxidation of XV to the corresponding diquinone, XVI. This was accomplished by acetylation of XV using isopropenyl acetate and p-toluenesulfonic acid (4 hours reflux) to give the diacetate XVII, mp 181-182° in 87% yield, along with a 6% yield of XVIII, mp 205-207°.

Reaction of XVII with lead tetraacetate in acetic acid with a trace of water to catalyze the reaction (16 hours, RT) led to a mixture containing 56% XIX, mp 233-235° dec., 28% XX, 9% XXI, mp 233-235° dec., and 1.6% XXII, mp 224-226° dec. The structures of XXI and XXII were confirmed by acetylation (isopropenyl acetate - p-toluenesulfonic acid, RT) to form pure XIX. Hydration of the acetylene derivative XIX by the method of Stavely[12] gave the corresponding ketone XXIII, mp 220-223°, in 70% yield, which on hydrolysis in refluxing methanol with 25% water and 2% concentrated HCl (40 hours, 60%) led to (±)-4-demethoxydaunomycinone[13], I. This material was spectrally identical with a sample kindly provided by Prof. A. S. Kende[14].

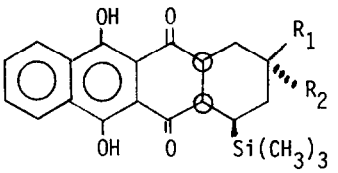
The minor ethynylation product, XI was carried through a similar series of reactions resulting, surprisingly in an improved yield of the desired cis-oxygenated products: 87% XVIII, 5% XIX, 6% XX, and 1.2% XXI.

However, a much more elegant procedure was discovered when we studied the lead tetraacetate oxidation of the dihydroxy anthraquinone derivative XV. A rapid oxidation to the corresponding diquinone XVI, occurred followed by a very slow displacement of the silyl group by acetate. Fortunately, this process could be accelerated by the addition of fluoride ion. Thus in practice XV was treated with 2 equivalents of lead tetraacetate in acetic acid in the presence of 5 equivalents of potassium fluoride. After 18 hours at room temperature the mixture was reduced with sodium bisulfite, leading to the diacetate XXIV[15], mp 245-248° in 79% yield and the monoacetate XXV, mp 245-248°, in 7% yield, both having the desired cis configuration. Hydration to XXVII, mp 243-245°, 96% yield, and hydrolysis, 85% yield, as above led to I. Further study on the mechanism of this reaction and on the application of these methods to the preparation of daunomycinone and adriamycinone are in progress.

It is important to note that the triacetate, XVIII did not react with lead tetraacetate indicating the importance of the neighboring phenolic hydroxyl function to the ease of the replacement. Under the same reaction conditions no acetoxylation of XXVIII[16] was observed.



VII



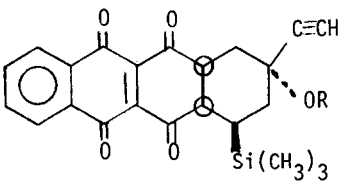
VIII. $R_1=R_2=OCH_3$

IX. $R_1,R_2=O$

X. $R_1=C\equiv CH$, $R_2=OH$

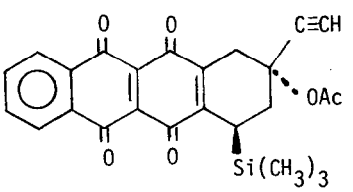
XI. $R_1=OH$, $R_2=C\equiv CH$

XII. $R_1=C\equiv CH$, $R_2=OAc$

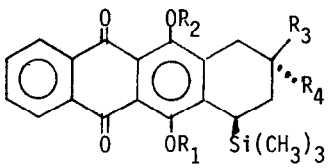


XIII. R=Ac

XIV. R=H



XVI

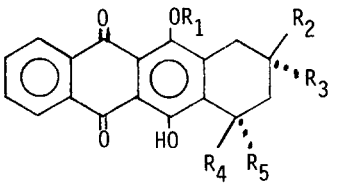


VI. $R_1=R_2=H$, $R_3,R_4=O$

XV. $R_1=R_2=H$, $R_3=C\equiv CH$, $R_4=OAc$

XVII. $R_1=H$, $R_2=Ac$, $R_3=C\equiv CH$, $R_4=OAc$

XVIII. $R_1=R_2=Ac$, $R_3=C\equiv CH$, $R_4=OAc$



XIX. $R_1=Ac$, $R_2=C\equiv CH$, $R_3=R_5=OAc$, $R_4=H$

XX. $R_1=Ac$, $R_2=C\equiv CH$, $R_3=R_4=OAc$, $R_5=H$

XXI. $R_1=Ac$, $R_2=C\equiv CH$, $R_3=OAc$, $R_4=H$, $R_5=OH$

XXII. $R_1=Ac$, $R_2=C\equiv CH$, $R_3=OH$, $R_4=H$, $R_5=OAc$

XXIII. $R_1=R_2=Ac$, $R_3=R_5=OAc$, $R_4=H$

XXIV. $R_1=R_4=H$, $R_2=C\equiv CH$, $R_3=R_5=OAc$

XXV. $R_1=R_5=H$, $R_2=C\equiv CH$, $R_3=R_4=OAc$

XXVI. $R_1=R_4=H$, $R_2=C\equiv CH$, $R_3=OAc$, $R_5=OH$

XXVII. $R_1=R_4=H$, $R_2=Ac$, $R_3=R_5=OAc$

XXVIII. $R_1=R_4=R_5=H$, $R_2=C\equiv CH$, $R_3=OAc$

References and Notes

1. a. A. S. Kende, Y. Tsay, and J. E. Mills, J. Am. Chem. Soc., 98, 1967, (1976), b. C. M. Wong, R. Schwenk, D. Popien, and T.-L. Lo, Can. J. Chem., 51, 466 (1973), c. T. H. Smith, A. N. Fujiwara, D. W. Henry, and W. W. Lee, J. Am. Chem. Soc., 98, 1969 (1976), d. R. D. Gleim, S. Trenbeath, R. S. D. Mittal, and C. J. Sih, Tetrahedron Lett., 3385 (1976), e. W. W. Lee, A. P. Martinez, T. H. Smith, and D. W. Henry, J. Org. Chem., 41, 2296 (1976), f. T. R. Kelly, J. W. Gillard, R. N. Goerner, and J. M. Lyding, J. Am. Chem. Soc., 99, 5513 (1977), g. A. S. Kende, D. P. Curran, Y. Tsay, and J. E. Mills, Tetrahedron Lett., 3537 (1977), h. P. W. Raynolds, M. J. Manning, and J. S. Swenton, Tetrahedron Lett., 2383 (1977), i. F. Suzuki, S. Trenbeath, R. D. Gleim, C. J. Sih, J. Am. Chem. Soc., 100, 2272 (1978).
2. U. S. 4,046,878, F. Arcamone et al, Cancer Treatment Reports, 60, 829 (1976).
3. All chiral compounds described in this report are racemates.
4. J. R. Kalman, J. T. Pinhey, and S. Sternhell, Tetrahedron Lett., 5369 (1972).
5. The advantage of a trimethylsilyl grouping in our Diels-Alder approach is obvious since a corresponding protected oxygen function would tend to eliminate rapidly upon hydrolysis of the enol acetate in the adducts.
6. R. A. Felix and W. P. Webber, J. Org. Chem., 37, 2323 (1972), A. G. Brook and J. M. Duff, Can. J. Chem., 51, 2024 (1973).
7. This compound is conveniently prepared by treating 1 mole of 3-butyn-2-ol in ether with 2 moles of butyl lithium then adding 2 moles of chlorotrimethylsilane and treating the product with methanol and dilute HCl to yield 4-(trimethylsilyl)-3-butyn-2-ol, bp 49-50°/0.2 mm (88%). Hydrogenation of this material in benzene with 0.5% quinoline over 5% palladium on barium sulfate gave cis-4-(trimethylsilyl)-3-buten-2-ol, bp 33-39°/0.3 mm 93%. Oxidation with Jones Reagent followed by isomerization with HCl in isopropanol gave trans-4-(trimethylsilyl)-3-buten-2-one (II) bp 165-169° (61%).
8. Independently from the Rochester group ref. 1a we had previously discovered that 2-acetoxybutadiene as opposed to 2-ethoxybutadiene gives rise to the desired linear tetracyclic Diels-Alder adduct with quinizarinquinone.
9. Recent results obtained by Dr. D. W. Hansen in our laboratories showed that direct alcoholysis of VII to IX was achieved in good yields by treatment with ethanolic magnesium ethoxide.
10. Separation was efficiently accomplished by a combination of fractional crystallization and "dry-column" chromatography, B. Loev and M. M. Goodman, Chem. Ind. (London), 2026 (1967), with 2% ethyl acetate-benzene on Mallinkrodt SilicAR CC-7 adsorbent.
11. Alternatively XIII could be prepared by oxidizing X to XIV,mp 183-187°, 87% yield, then acetylation in 93% yield.
12. H. E. Stavely, J. Am. Chem. Soc., 63, 3127 (1941).
13. Wide variations in melting point behavior were observed for this compound, some samples melting at ca 167-170°, some at 197-200°, and others showing a slow transition from lower to higher melting form. All melting points in this report were taken on a Fisher-Johns block and are uncorrected.
14. Prepared by a route similar to his preparation of (±)-daunomycinone ref. 1a.
15. Examination of the mother liquors indicated ca 5% more XXIV with a similar amount of the trans isomer (XXV).
16. Prepared by the method of Kende, ref. 1a, or by desilylation of XV which readily occurs in pyridine solution with a small amount of methanol.

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