phenylpropan-1-one, 71908-03-7; *threo*-2-(hydroxyphenylmethyl)-1-phenylpropan-1-one, 71908-02-6; *erythro*-2-(hydroxyphenylmethyl)-1-mesitylpropan-1-one, 61878-66-8; *threo*-2-(hydroxyphenylmethyl)-1-mesitylpropan-1-one, 61878-67-9; *erythro*-3-hydroxy-2,4-dimethyl-1-(2,4,6-trimethylphenyl)pentan-1-one, 71699-37-1; *threo*-3-hydroxy-2,4-dimethyl)-1-(2,4,6-trimethylphenyl)pentan-1-one, 71699-38-2; *erythro*-2-(hydroxyphenylmethyl)-1-mesitylpropan-1-one, 61878-66-8; *threo*-2-(hydroxyphenylmethyl)-1-mesitylpropan-1-one, 61878-67-9; *erythro*-2-(1-hydroxy-2-methylpropyl)cyclohexan-1-one, 81640-04-2; *erythro*-2-(1-hydroxy-2-methylpropyl)cyclopentan-1-one, 26620-52-0; *threo*-2-(1-hydroxy-2-methylpropyl)cyclopentan-1-one, 26662-85-1; *erythro*-2-(2-methyl-1-(trimethylsiloxy)propyl)cyclopentanone, 77504-15-5; *threo*-2-(2-methyl-1-(trimethylsiloxy)propyl)cyclopentane, 84624-40-8; *erythro*-3-(hydroxyphenylmethyl)-3-phenylpropan-2-one, 60418-00-0; *threo*-3-(hydroxyphenylmethyl)-3-phenylpropan-2-one, 60418-02-2; *erythro*-2-(α-hydroxybenzyl)cyclopentanone, 43108-70-9; *threo*-2-(α-hydroxybenzyl)cyclopentanone, 43108-71-0; *erythro*-2-(α-hydroxybenzyl)cyclohexanone, 13161-18-7; *threo*-2-(α-hydroxybenzyl)cyclohexanone, 42052-56-2; *erythro*-2-(α-hydroxy-*p*-methoxybenzyl)cyclohexanone, 84624-41-9; *threo*-2-(α-hydroxy-*p*-methoxybenzyl)cyclohexanone, 84624-42-0; *erythro*-2-(α-hydroxy-*p*-nitrobenzyl)cyclohexanone, 71444-29-6; *threo*-2-(α-hydroxy-*p*-nitrobenzyl)cyclohexanone, 71444-30-9; *erythro*-2-(α-hydroxy-*m*-nitrobenzyl)cyclohexanone, 04624-43-1; *threo*-2-(α-hydroxy-*m*-nitrobenzyl)cyclohexanone, 84624-44-2; *erythro*-α-(2-oxocyclohexyl)furanmethanol, 84624-45-3; *threo*-α-(-2-oxocyclohexyl)-furanmethanol, 84624-46-4; benzyl methyl ketone, 103-79-7; chlorotrimethylsilane, 75-77-4; acetic anhydride, 108-24-7; methyl iodide, 33574-02-6; cyclopropylmethyl iodide, 33574-02-6; 5-hexenyl iodide, 18922-04-8; allyl bromide, 106-95-6; benzyl bromide, 100-39-0; butyl iodide, 542-69-8; methyl bromoacetate, 96-32-2; benzaldehyde, 100-52-7; isobutylaldehyde, 78-84-2; butanol, 123-72-8; π-anisaldehyde, 123-11-5; *p*-nitrobenzaldehyde, 555-16-8; furfural, 98-01-1.

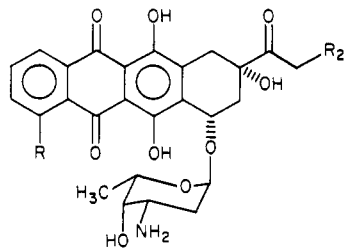
An Improved Route to 4-Demethoxydaunomycinone. A-Ring Functionalization and Resolution Studies of Tetracyclic Precursors

Domingo Domínguez, Robert J. Ardecky, and Michael P. Cava*

Contribution from the Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104. *Received July 23, 1982*

Abstract: A detailed study has been made of the conversion of the readily prepared 4-demethoxy-7,9-dideoxydaunomycinone (**4**) and its dimethyl ether (**5**) into 4-demethoxydaunomycinone (**24**). Procedures have been developed that are suitable for the preparation of **24** in multigram quantities. In addition, racemic 4-demethoxy-7-deoxydaunomycinone (**16**) has been resolved into its enantiomers by using Enders' hydrazine reagent.

The discovery of the improved antineoplastic activity of the synthetic anthracycline 4-demethoxydaunomycin (**1**),[1] as compared



1, $R_1 = R_2 = H$
2, $R_1 = OMe$; $R_2 = H$
3, $R_1 = OMe$; $R_2 = OH$

with the naturally occurring daunomycin (**2**) and adriamycin (**3**), has stimulated considerable synthetic effort toward the corresponding aglycon 4-demethoxydaunomycinone (**24**).[2] In many of these studies, the tetracyclic red ketone **4** was the target molecule.[3] Early work by Sih[3f] provided a method of 9-hydroxylation, and Wong,[15] Kende[4], and Smith[5] have described the introduction of the second hydroxy group in the 7-position of the A-ring. In our hands the above-mentioned hydroxylation methods were not satisfactory for large-scale preparations of the desired aglycon **24**. Because of this, we decided to reinvestigate the problem of the ring A functionalization of anthracyclinones. Here we report detailed procedures for the introduction of the *cis*-7,9-diol functionality of the A-ring, in addition to the resolution of the racemic tetracyclic hydroxy ketone **16**, a result which allows the preparation of optically active aglycons.

Results and Discussion

The trapping by methyl vinyl ketone of transient *o*-quinodimethane derivatives of bis(bromomethyl)quinizarins provided us with a practical and very efficient route for the preparation of large quantities of the tetracyclic ketones **4** to **6**.[6] With these compounds in hand, we addressed the next challenge of the anthracyclinone synthesis, i.e., the functionalization of the A-ring by a stepwise introduction of the *cis*-diol functionality by procedures applicable to larger scale syntheses.

(a) 9-Hydroxylation. We have earlier reported the one-step preparation of 7-deoxyaglycones using 3-acyloxy-3-buten-2-ones as trapping agents in our *o*-quinodimethane synthesis of anthracyclinones. This procedure gave variable yields (2–46%) of 9-oxy derivatives, the results being highly dependent on the electronic properties of both the diene and the dienophile.[6] Since the above procedure can only be applied for that particular Diels–Alder

(1) Arcamone, F.; Bernardi, L.: Giardino, P.; Patelli, B.; DiMarco, A.; Casazza, A. M.; Pratessi, G.; Reggiani, P. *Cancer Treat. Rep.* **1976**, *60*, 829.
(2) For a recent comprehensive review, see: Arcamone, F. "Doxorubicin"; Academic Press: New York, 1981.
(3) (a) Gleim, R. D.; Trenbeath, S.; Mittall, R. S.; Sih, C. J. *Tetrahedron Lett.* **1976**, 3385. (b) Boatman, R. J.; Whitlock, B. J.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1977**, *99*, 4822. (c) Suzuki, F.; Gleim, R. D.; Trenbeath, S.; Sih, C. J. *Tetrahedron Lett.* **1977**, 2303. (d) Kerdesky, F. A. J.; Cava, M. P. *J. Am. Chem. Soc.* **1978**, *100*, 3635. (e) Kerdesky, F. A. J.; Ardecky, R. J.; Lakshmikantham, M. V.; Cava, M. P. *Ibid.* **1981**, *103*, 1992. (f) Suzuki, F.; Trenbeath, S.; Gleim, R. D.; Sih, C. J. *J. Org. Chem.* **1978**, *43*, 4159. (g) Ashcroft, A. E.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1981**, 1075.
(4) (a) Kende, A. S.; Tsay, Y.; Mills, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 1967. (b) Kende, A. S.; Curran, D. P.; Tsay, Y.; Mills, J. E. *Tetrahedron Lett.* **1977**, 3537.
(5) Smith, T. H.; Fujiwara, A. N.; Henry, D. W.; Lee, W. W. *J. Am. Chem. Soc.* **1976**, *98*, 1969. See also: Smith, T. H.; Fujiwara, A. N.; Lee, W. W.; Wu, H. Y.; Henry, D. W. *J. Org. Chem.* **1977**, *42*, 3653.
(6) Ardecky, R. J.; Dominguez, D.; Cava, M. P. *J. Org. Chem.* **1982**, *47*, 409.

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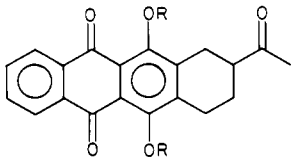
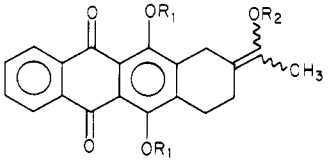
approach for the construction of the A-ring, we were interested in a much more general procedure, i.e., the 9-hydroxylation of the readily prepared common intermediate 4-demethoxy-7,9-dideoxydaunomycinone.[3]

Our initial experiments involved an oxygenation of the enolate of the ketone (**5**) followed by in situ reduction of the hydroperoxide, the hydroxy ketone **19** being obtained in 55% yield.[3d] Subsequent attempts to scale up this reaction resulted in very poor yields, complex mixtures of compounds being obtained. This may be due to the acidity of the benzylic protons, which may cause interference with a selective oxygenation of the thermodynamic enolate of the acetyl side chain.

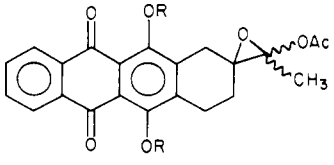


4, R = H
5, R = Me
6, R = Ac

A very well-known and general procedure for the introduction of an α-hydroxy group to a ketone, long used in the 17-hydroxylation of 20-ketosteroids, involves an acid-catalyzed enol acetylation, followed by epoxidation and hydrolytic opening of the resulting epoxy acetate. This approach has already been reported in the daunomycinone series, using a very large excess of *p*-toluenesulfonic acid as the catalyst for the initial enolization.[3f] Our attempts to carry out this reaction in larger scale preparations failed to give practical yields of the enol acetate of **4** even in refluxing acetic anhydride in the presence of equimolar amounts of *p*-TsOH. The diacetoxy ketone **6** was recovered in 80% yield, even after prolonged heating. In view of the above result, we decided to investigate different catalysts and conditions in order to work out optimal conditions for the enol acetylation step. After considerable experimentation, we found that the perchloric acid catalyzed reaction of **4** in a mixture of Ac_2O/Cl_4C at room temperature[7] gave the best results. Examination of the course of the reaction by ^1H NMR spectroscopy showed the presence of a mixture of both enol acetate **7** and ketone **6**, the best ratio (7:3, respectively) being obtained after 8 h of stirring. Longer reaction times, addition of isopropenyl acetate to the reaction mixture, or heating did not improve this ratio. The ^1H NMR spectrum showed **7** to be a (1:1) mixture of both geometrical isomers, which was epoxidized with *m*-CPBA in 95% yield. Mild alkaline hydrolysis of the epoxide isomers **12** with dilute sodium hydroxide gave a practically quantitative yield of hydroxy ketone **16**. Alternatively, different hydrolytic conditions gave protected 9-oxy derivatives. Thus, *p*-toluenesulfonic acid treatment of the epoxide **12** in aqueous conditions gave the diacetoxy ketone **17** in 85% yield. When this reaction was carried out in warm acetic anhydride, a quantitive yield of the rearranged[8] triacetoxy derivative (**18**) was obtained.



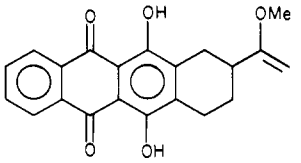
7, $R_1 = R_2 = Ac$
8, $R_1 = Me$; $R_2 = Ac$
9, $R_1 = OH$; $R_2 = Me_3Si$
10, $R_1 = OH$; $R_2 = Me$



12, R = Ac
13, R = Me

Under the described conditions, multigram preparations of hydroxy ketones **16** and **19** were carried out without isolation of intermediates in 70–75% overall yields, based on recovered starting materials **4** and **5** (25–30%), easily separated from the hydroxy compounds by chromatography.

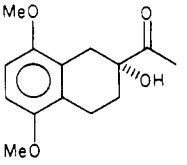
In an attempt to overcome the difficulty imposed by the incomplete enolization of the starting ketones, we decided to investigate the preparation of other enol derivatives such as the trimethylsilyl and methyl ethers **9** and **10**. Experiments to prepare the first one under a large variety of conditions ($Et_3N/DMF/Me_3SiCl$, $LDA/THF/Me_3SiCl$, $HNa/DMe/Me_3SiCl$, $(Me_3Si)_2NLi/THF/Me_3SiCl$, $Et_3N/C_6H_6/CF_3SO_3Me_3Si$) were completely unsuccessful. On the other hand, the methyl enol ether could in fact be prepared from the dimethylacetal of ketone **4**, by methanol elimination. This was carried out in two different ways (xylene/*p*-TsOH/reflux or pyridine/P_2O_5/100 °C), giving in both cases similar mixtures (3:1, by ^1H NMR spectroscopy) of isomeric methyl enol ethers. The undesired less substituted **11** was the major product (vinylic protons at 3.96 and 3.99, doublets, J = 2.5 Hz). Attempts to increase the amount of the more substituted **10** by prolonged refluxing of the mixture with *p*-TsOH or by treatment with iodine at room temperature did not give any appreciable change in composition.



11

Another alternative procedure that was considered was based upon Barton's new elaboration of the hydroxyacetyl side chain of corticosteroids.[9] Our attempts to carry out this sequence starting with the oximes of **4** and **5** afforded very complex mixtures of compounds with none of the desired 9-hydroxy ketones being obtained.

(b) Resolution of the Hydroxy Ketone 16. In spite of the fact that only 7(*S*),9(*S*)-anthracyclines are biologically active,[2] not much effort has been expended in the preparation of the optically active aglycons. Such compounds would not only avoid the very difficult separation of diastereomeric products in the final glycosidation step (pairs of α and β anomeric compounds), but would also save the valuable sugar moiety. So far, the only published procedures make use of an optically active tetralin as an AB synthon, i.e., **14**, that has been prepared by resolution of racemic material or by asymmetric synthesis.[10] In addition, two examples



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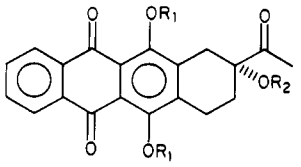
(7) Attenburrow, J.; Connett, J. E.; Graham, W.; Oughton, J. F.; Ritchie, A. C.; Wilkinson, P. A. *J. Chem. Soc.* **1961**, 4547.

(8) Williamson, K. L.; Coburn, J. I.; Herr, M. F. *J. Org. Chem.* **1967**, *32*, 3934.

(9) Boar, R. B.; McGhie, F. J.; Robinson, M.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1242.

(10) (a) Arcamone, F.; Bernardi, L.; Patelli, B.; DiMarco, A. German Patent 2 601 785, 1976. (b) Broadhurst, M. J.; Hassall, G. H.; Thomas, G. J. *J. Chem. Soc., Chem. Commun.* **1982**, 158. (c) Terashima, S.; Jew, S. S.; Koga, K. *Tetrahedron Lett.* **1978**, 4937. (d) Terashima, S.; Tanno, N.; Koga, K. *Ibid.* **1980**, 2753. (e) Warrener, R. N.; Gee, P. S.; Russell, R. A. *J. Chem. Soc., Chem. Commun.* **1981**, 1100.

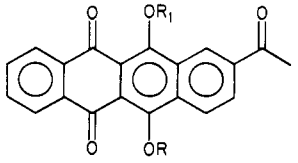
of resolution at the tetracyclic stage are to be found in the patent and thesis literature.[11] In view of the readily availability of the hydroxy ketone **16**, we carried out some studies on the resolution



16, $R_1 = R_2 = H$
17, $R_1 = Ac; R_2 = H$
18, $R_1 = R_2 = Ac$
19, $R_1 = Me; R_2 = H$
20, $R_1 = Me; R_2 = Ac$

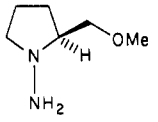
of this compound, since once resolved, it would give the desired (+)-demethoxydaunomycinone after a stereoselective 7-hydroxylation.

α-(−)-Phenethylamine was the first resolving agent we chose. To our surprise, no reaction took place with (±)-**16** under the standard reaction conditions for imine formation. Under drastic conditions, complex mixtures of compounds were formed, the fully aromatic compound **29** being present in the reaction mixture. This



29, R = H
30, R = Me

lack of reactivity, which contrasts with the clean formation of the corresponding oxime, made us turn to other resolving agents having a more reactive hydrazine functionality. We found that Enders' reagent (**15**)[12] readily reacts with ketone **16** in the presence of



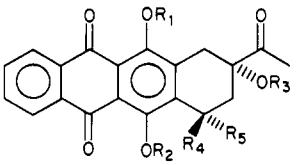
15

acid to give a mixture of diastereomeric hydrazones in 95% yield, as shown by two methyl peaks at δ 2.04 and 2.02 in the high-resolution ^1H NMR spectrum.[13] Fractional crystallization from acetonitrile gave a single compound responsible for the 2.04 methyl signal. Hydrolysis with diluted acetic acid in THF at room temperature followed by chromatography gave (*R*)-(−)-4-demethoxy-7-deoxydaunomycinone (**16**), in 87% enantiomeric excess.[14] It may be noted that this appears to be the first application of Enders' reagent as a resolving agent.

(c) 7-Hydroxylation. With the 9-oxy compounds **16–20** in hand, we next addressed our attention to the introduction of the 7-hydroxyl group. The introduction of this function was first achieved by Wong[15] by bromination (NBS) of the ethyleneacetal derived from **19**, through uncharacterized and unstable bromo compounds which were methanolized to the corresponding 7-methoxy derivatives. Later on, others[4,5] applied this procedure to the synthesis of aglycons; in no case was a 7-bromo derivative isolated, presumably due to its instability. It should be noted that in this work, compounds containing free hydroxyl groups were used as starting materials, limiting their utility to small-scale experiments as a consequence of their low solubility. In addition, reaction of 7-deoxy aglycons with several bromination agents (Br_2, NMe_4Br_3, NBS) have been reported[5] to cause problems like unreactivity and aromatization.[16]

We felt that a practical procedure should involve either a direct oxidation of the C-7 benzylic position or a modified bromination reaction suitable for preparative work, without reproducibility problems. Attempts to oxidize the benzylic position of triacetoxy ketone **18** with excess of lead tetraacetate in refluxing benzene or acetic acid,[17] or with ceric ammonium nitrate in refluxing acetic acid,[18] gave only recovered starting material (NMR and TLC). Other oxidation procedures which were checked with 2-methylanthraquinone as a model ($(PhCO_2)_2SeO$,[19] SeO_2/Ac_2O, $PhCO_3$-*t*-Bu/CuBr[20]) gave no oxidized products, indicating a surprising inertness of the benzylic position of the anthraquinone system to oxidation.

We next addressed our attention to the search for a modified bromination procedure, the ideal situation being the utilization of a substrate and reaction conditions which would allow us to achieve the preparation of 7-bromo derivatives on a preparative scale and in reproducible yields. Our first experiments with CCl_4-soluble compounds **17**, **19**, and **12** using 1,3-dibromo-5,5-dimethylhydantoin as the brominating agent, gave very complex mixtures, as shown by TLC analysis. Fortunately, the same reaction starting with triacetate **18** afforded a nicely crystalline major product (80%), mp 216–17 °C, identified as the 7-bromo derivative **21**. The high-resolution proton spectra of this compound showed sharp singlets for the aliphatic acetoxy and methyl groups, indicative of the presence of a single stereoisomer. The related dimethoxy acetoxy compound **20** gives a single crystalline bromide in 85% yield, proving the importance of the 9-acetoxy group in the successful regioselective bromination. This suggests the participation of the axial acetoxy group at C-9 in the stabilization of the C-7 benzyl radical, resulting in a probable trans stereochemistry in the final bromides **21** and **22**. In the bromination of **18** a minor product was detected, both spectroscopically and by TLC, but it was too unstable to be isolated. This compound seems to be the cis isomer **23**, with the bromine atom is an axial position, which can easily lose HBr by an anti elimination.



21, $R_1 = R_2 = R_3 = Ac; R_4 = Br; R_5 = H$
22, $R_1 = R_2 = Me; R_3 = Ac; R_4 = Br; R_5 = H$
23, $R_1 = R_2 = R_3 = Ac; R_4 = H; R_5 = Br$
24, $R_1 = R_2 = R_3 = R_4 = H; R_5 = OH$
25, $R_1 = R_2 = R_3 = R_5 = H; R_4 = OH$
26, $R_1 = R_3 = Ac; R_2 = R_4 = H; R_5 = OAc$
27, $R_1 = R_3 = Ac; R_2 = R_5 = H; R_4 = OAc$
28, $R_1 = R_2 = R_3 = Ac; R_4, R_5 = H, OAc$

The transformation of **21** to 4-demethoxydaunomycinone (**24**) was studied by three different routes in search for an overall stereoselective replacement of bromine by hydroxide, to give the desired *cis*-diol functionality. Thus, silver trifluoroacetate in trifluoroacetic acid treatment of **21** at room temperature for 5

(11) (a) Kende, A. S.; Mills, J. E.; Tsay, Y. U. S. Patent 4021457, 1977. (b) Mills, J. E. PhD Thesis, University of Rochester, 1977.
(12) Enders, D.; Eichenauer, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 549.
(13) Separation of compounds showed that these peaks were due to diastereomeric hydrazones and not to geometric isomers.
(14) As determined by comparison with the reported value $[\alpha]_D^{20}$ −87°: Arcamone, F.; Bernardi, L.; Patelli, B.; Giardino, P.; DiMarco, A.; Casazza, A. M.; Soranzo, C.; Pratesi, G. *Experientia* **1978**, *34*, 1255.
(15) (a) Wong, C. M.; Popien, D.: Schwenk, R.; Raa, J. T. *Can. J. Chem.* **1971**, *49*, 2712. (b) Wong, C. M.; Schwenk, R.; Popien, D.; Tse-Lok, H. *Ibid.* **1973**, *51*, 466.
(16) Some alternatives have been reported where the introduction of a (latent) 7-oxy functionality is achieved earlier in the synthesis. See, for example: Jackson, D. A.; Stoodley, R. J. *J. Chem. Soc., Chem. Commun.* **1981**, 478 and references cited therein.
(17) Dhekne, V. V.; Rao, A. S. *Synth. Commun.* **1978**, *8*, 135.
(18) Syper, L. *Tetrahedron Lett.* **1966**, 4493.
(19) Nerdel, F.; Kleinvrachter, J. *Naturwissenschaften* **1955**, 42; *Chem. Abstr.* **1957**, *51*, 11151*f*.
(20) Kharash, M. S.; Sosnovsky, G.; Yang, N. C. *J. Am. Chem. Soc.* **1959**, *81*, 5819.

h, followed by methanolysis, showed by TLC the presence of three main products. The ^1H NMR spectrum of the crude reaction mixture indicated that the aromatic acetoxy groups had been hydrolyzed, but peaks at δ 2.03, 2.07, and 2.10 suggested that no transesterification of the aliphatic acetoxy group at C-9 had taken place. When the crude product from the silver trifluoroacetate treatment (room temperature/2 h) was directly hydrolyzed with dilute sodium hydroxide at room temperature for 2 h, followed by silica gel chromatography, 4-demethoxydaunomycinone (**24**) and the epi isomer **25** were obtained in 41 and 20% yields, respectively.[21] This result contrasts sharply with the reported bromination of **16**, which gives, after hydrolysis, epi-**25** as the major compound.[4b] On the other hand, treatment of bromide **22** with $AgOOCCF_3$/TFA gave a complex mixture of compounds,[22] which was demethylated with $AlCl_3$, followed by alkaline hydrolysis, giving a (1:2) mixture of **24** and **25**.

Direct treatment of **21** with dilute alkali in the cold was shown to be nonsterospecific, giving a crude mixture of **24** and **25** in a ratio of approximately 1:1, as deduced by ^1H NMR integration of the hydrogen-bonded phenolic groups (13.59 and 13.31 in **24**; 13.94 and 13.32 in **25**). The fully aromatic tetracyclic compound **29** was present in the above mixture to the extent of about 20%, as shown by additional hydroxyl peaks at 14.96 and 15.10. Equilibration of the above mixture with TFA[4] gave 29% of **29**, 48% of **24**, and 9% of **25**.

On the other hand, reaction of bromide **21** with silver acetate in warm acetic acid gave a complex mixture of compounds, three of them being separated by preparative chromatography; these were identified as the tetraacetoxy derivative **28** (27%, mixture of isomers) and the triacetoxy isomers **26** (26%, mp 219–221, lit.[27] mp 220–223 °C) and **27** (13%, mp 203–204). The latter two products are derived by a participation of the aromatic acetoxy group adacent to the bromine atom being substituted. Similar acid-catalyzed acetate shifts from the oxygen at C-6 to C-7 have been observed in related anthracyclinone systems.[23] As expected, much cleaner results were obtained when the above crude mixture was directly acetylated, giving the tetraacetoxy derivative **28** in 61% yield, after chromatographic purification. The ^1H NMR spectrum of this material showed two singlets at δ 2.25 and 2.17 (3:2 ratio, respectively), assigned to the 9-acetyl side chain. The major isomer was assumed to have the cis configuration by the similarity of its chemical shift with the value (δ 2.25) reported for a similar *cis*-7,9-diacetoxyanthracyclinone derivative.[23] Acid hydrolysis of the above tetraacetates (**28**) with dilute hydrochloric acid took place slowly, giving a crude mixture (ca. 85%) of 4-demethoxydaunomycinone (**24**) and its 7-epi isomer **25** (2:1 ratio, respectively), less than 5% of the bis(anhydro) derivative **29** being present, as shown by ^1H NMR spectroscopy. Epimerization of this mixture, followed by chromatographic separation, gave 44% of **24** and 9% of **25** from **28**.

Thus we have accomplished the total synthesis of 4-demethoxydaunomycinone (**24**) by a practical and preparatively useful method by functionalization of the A-ring of the readily available ketones **4** and **5**. The overall yield of (±)-**24** is 26% and 30% from **4** and **5**, respectively. When carried through the resolution stage it is 8% of (+)-**24** (87% ee), based on **4**. Compounds **21** and **22** have been isolated and characterized, representing the first examples of pure, stable 7-bromo derivatives. These bromo compounds are not only valuable intermediates in the sythesis of 4-demethoxydaunomycinone (**24**), but they are also potentially useful intermediates in the synthesis of new 7-substituted analogues of 4-demethoxydaunomycin (**1**). Investigations in this direction are currently being undertaken in our laboratories.

(21) Identified by direct comparison with authentic samples kindly provided by J. S. Swenton of The Ohio State University.

(22) Subsequent qualitative experiments with 2,3-dimethylquinizarin dimethyl ether showed that slow demethylation takes place when treated with TFA at room temperature, explaining the result observed with **22** as a consequence of partial demethylation.

(23) Arcamone, F.; Cassinelli, G.; DiMatteo, F.; Forenza, S.; Ripamonti, M. C.; Rivola, G.; Vigerani, A.; Clardy, J.; McCabe, T. *J. Am. Chem. Soc.* **1980**, *102*, 1462.

Experimental Section

General Information. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Mass, infrared (KBr), and ultraviolet spectra were determined with Perkin-Elmer 270B, 137, and 202 spectrometers, respectively. NMR spectra were recorded on Varian-60, EM-300, and Bruker 250-MHz FT instruments, in $CDCl_3$ solutions (unless otherwise stated) containing Me_4Si as internal standard and are reported in δ units. Elemental analyses were performed by Galbraith Laboratories. All organic extracts were washed and dried over anhydrous Na_2SO_4 prior to evaporation. Compounds **4**, **5** and **6** were prepared as previously described, by reaction with methyl vinyl ketone of the corresponding anthraquinone-derived *o*-quinodimethane.[3e,6] Higher yields (85%) than earlier reported (69%)[3e] were obtained in multigram (16 g) preparations of **4** when the crude reaction mixture was subjected to chromatographic purification [SiO_2, C_6H_6 followed by CH_2Cl_2–EtOAc (5%)]. Brominations were performed on a well-illuminated lab bench and were considerably accelerated by sun lamp illumination.

8-Acetyl-6,8,11-trihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (16). To a stirred suspension of 9 g of ketone (**4**) in a mixture of carbon tetrachloride (180 mL) and acetic anhdyride (100 mL) at room temperature was added 0.35 mL of perchloric acid (62%). The homogeneous yellow solution was stirred for 8 h. Solid sodium bicarbonate (2 g) was added, and the mixture was stirred for 10 min and filtered. The filtrate was concentrated in vacuo to give a syrup that was taken up in CH_2Cl_2 and washed with a cold aqueous saturated sodium bicarbonate solution. The organic phase was concentrated. Traces of acetic anhydride were eliminated by addition of EtOH–CH_2Cl_2 and evaporation in vacuo. The crude mixture of enol acetate **7** and diacetoxy ketone **6** was obtained as a yellow foam (12 g), which was dissolved in CH_2Cl_2 (100 mL) and treated with an excess of *m*-chloroperbenzoic acid (5.6 g, prewashed with Na_2HPO_4[24]) in the presence of a disodium hydrogen phosphate buffer (160 mL of a 5% aqueous solution). After 3 h at room temperature the organic phase was separated, successively washed with dilute sodium sulfite and sodium bicarbonate, dried, and concentrated, affording 12 g of a crude mixture of epoxide **12** and diacetoxy ketone **6**. This was dissolved in a mixture of THF (150 mL), H_2O (120 mL), and 55 mL of sodium hydroxide (10%) and stirred at room temperature, under nitrogen, for 40 min. Acidification with 12% HCl (color change to dark red) and extraction with CH_2Cl_2, followed by silica gel chromatography (CH_2Cl_2) gave ketone **4** (2.41 g, 27%), mp 199–201 °C, and [CH_2Cl_2–EtOAc (5%)] hydroxy ketone **16** (4.92 g, 52%), mp 202–203 °C (MeOH–CH_2Cl), identified by comparison with authentic samples.[6]

Enol Acetate 7. The crude mixture obtained after acetylation of 2 g of ketone (**4**) was chromatographed [SiO_2, CH_2Cl_2–EtOAc (5–15%)] giving pure **7** (1.46 g, 53%) and additional fractions containing mixtures of **7** and **6**[6] (1.2 g). Compound **7** was shown by NMR spectroscopy to be a mixture of geometrical isomers (1:1): mp 95–100 °C (hexane); NMR δ 1.95 (bs, 3 H, CH_3), 2.18 and 2.20 (s, 3 H, OAc), 2.50–2.54 (6 H, ArOAc), 7.78 (m, 2 H, Ar), 8.20 (m, 2 H, Ar); UV–vis λ_{max} (EtOH) 258 (log ϵ 4.47) 276 (4.16), 339 nm (3.36); MS, *m/e* 420 (M – CH_2CO, 33), 378(51), 337 (56), 336 (96), 334 (100); IR 1760 (b, OAc), 1670 (quinone), 1585 (Ar) cm^{-1}.

Epoxy Acetate 12. Enol acetate **7** (1.20 g) was epoxidized as described in the general procedure. Trituration with hexane gave epoxide **12** (1.16 g, 94%) as a mixture of isomers (1:1): mp 159–160 °C; NMR δ 1.77 and 1.79 (s, 3 H, CH_3), 2.08 and 2.12 (s, 3 H, OAc), 2.47, 2.49, 2.50, and 2.51 (s, 6 H, ArOAc), 7.74 (m, 2 H, Ar), 8.14 (m, 2 H, Ar); IR 1765 (ArOAc), 1680 (quinone), 1590 cm^{-1} (Ar); UV–vis λ_{max} (EtOH) 258 (log ϵ 4.71), 275 (4.22), 338 nm (3.83); MS, m/e 436 (M – CH_2CO, 2), 394 (10), 376 (10), 334 (100), 309 (22), 291 (30). Anal. Calcd for $C_{26}H_{22}O_9$: C, 65.27; H, 4.63. Found: C, 65.16; H, 4.75.

(*R*)-(−)-8-Acetyl-6,8,11-trihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (16). A solution of racemic hydroxy ketone **16** (0.50 g), *p*-toluenesulfonic acid (0.01 g), and Enders' hydrazine (**15**, 1.0 mL) in 20 mL of toluene was heated to reflux for 1 h. The solvent was evaporated and the residue washed with methanol and filtered to give a mixture of hydrazone diasteromers as a red powder (0.63 g, 95%). Five crystallizations from acetonitrile gave the less soluble isomer as shining red crystals (0.098 g, 31%), mp 184–186 °C; NMR δ 1.6–3.51 (m, 15 H, CH_2 and CH), 2.04 (s, 3 H, CH_3), 3.37 (s, 3 H, OCH_3), 5.25 (s, 1 H, OH), 7.81 (m, 2 H, Ar), 8.32 (m, 2 H, Ar), 13.51 (s, 1 H, OH), 13.52 (s, 1 H, OH); MS, *m/e* 464 (M^+, 1), 401 (38), 332 (49), 309 (88), 70 (100). Anal. Calcd for $C_{26}H_{28}O_6N_2$: C, 67.23; H, 6.07; N, 6.03. Found: C, 67.02; H, 6.04; N, 5.95.

The crystalline hydrazone (10 mg) was dissolved in a mixture of THF (2 mL), acetic acid (5 drops), and water (5 drops), and the solution was stirred at room temperature for 1 h. The solvent was evaporated and the

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residue was chromatographed (SiO_2, CH_2Cl_2/1% MeOH) to give (−)-**16** (7.5 mg, 98%), mp 204–208 °C, $[\alpha]_D$ −76° (lit.[14] $[\alpha]_D$ −87°). The NMR and IR spectra were identical with those of racemic **16**.

8-Acetyl-8-Hydroxy-7,8,9,10-tetrahydro-6,11-diacetoxy-5,12-naphthacenedione (17). A solution of **12** (0.2 g, 0.42 mmol) and *p*-TsOH·H_2O (0.095 g, 0.5 mmol) in a mixture of THF (15 mL) and H_2O (3 mL) was stirred at room temperature for 24 h. The THF was removed, the residue taken up in CH_2Cl_2 and washed with aqueous solution bicarbonate and water. Chromatography [SiO_2, CH_2Cl_2–EtOAc (10%)] and crystallization (CH_2Cl_2–hexane) gave pale yellow needles of **17** (0.154 g, 85%): mp 212 °C; NMR δ 1.95 (m, 2 H, CH_2), 2.34 (s, 3 H, CH_3), 2.50 (s, 3 H, ArOAc) 2.52 (s, 3 H, ArOAc), 2.7–3.1 (m, 4 H, benzyl), 3.62 (bs, 1 H, OH), 7.74 (m, 2 H, Ar), 8.16 (m, 2 H, Ar); IR 1785 (ArOAc), 1720 ($COCH_3$), 1680 (quinone), 1585 cm^{-1} (Ar); UV–vis λ_{max} (EtOH) 257 (log ε 4.32), 277 (3.68), 340 nm (3.24); MS, *m/e* 394 (M − CH_2CO, 4), 352 (30), 334 (13), 309 (100), 291 (13). Anal. Calcd for $C_{24}H_{20}O_8$: C, 66.05; H, 4.62. Found: C, 65.91; H, 4.69.

8-Acetoxy-8-acetyl-7,8,9,10-tetrahydro-6,11-diacetyoxy-5,12-naphthacenedione (18). Method A. A solution of epoxide **12** (0.83 g) and a catalytic amount of *p*-TsOH·H_2O (50 mg) in 30 mL of acetic anhydride was stirred at room temperature for 18 h. The solvent was evaporated in vacuo and the residue crystallized from MeOH–CH_2Cl_2, giving pale yellow crystals of triacetoxy ketone **18** (0.86 g, 100%): mp 242–43 °C (lit.[25] mp 244–45 °C); NMR δ 1.92 and 2.44 (m, 2 H, CH_2), 2.05 (s, 3 H, OAc), 2.23 (s, 3 H, CH_3), 2.8–3.3 (m, 4 H, benzylic), 2.53 (s, 3 H, ArOAc), 2.54 (s, 3 H, ArOAc), 7.74 (m, 2 H, Ar) 8.16 (m, 2 H, Ar); IR 1770 (ArOAc), 1740 (OAc), 1720 ($COCH_3$), 1670 (quinone), 1585 cm^{-1} (Ar); UV–vis λ_{max} (EtOH) 257 (log ε 4.11), 276 (3.61), 336 nm (3.22); MS, *m/e* 436 (M − CH_2CO,2), 394 (9), 376 (11), 334 (100), 316 (18), 309 (18). Anal. Calcd for $C_{26}H_{22}O_9$: C, 65.27; H, 4.62. Found: C, 64.96; H, 4.62.

Method B. To a suspension of trihydroxy ketone **16** (1.48 g) in 75 mL of Ac_2O was added a catalytic amount (0.1 mL) of concentrated H_2SO_4. The resulting mixture was heated at 90 °C for 6 h. The solvent was removed in vacuo and the residue crystallized from MeOH–CH_2Cl_2 giving **18** (1.89 g, 95%), mp 242–243 °C.

8-Acetyl-8-hydroxy-7,8,9,10-tetrahydro-6,11-dimethoxy-5,12-naphthacenedione (19). To a stirred suspension of 3.0 g of ketone (**5**) in a mixture of 40 mL of acetic anhydride and 50 mL of carbon tetrachloride at room temperature was added 0.2 mL of perchloric acid. The reaction was stirred for 8 h and worked up as described previously for compound **16**. Epoxidation (2.2 g of *m*-CPBA) and hydrolysis gave a residue which was chromatographed (SiO_2, CH_2Cl_2–5% EtOAc), giving 0.7 g (26%) of starting ketone **5** and 1.75 g (56%) of hydroxy ketone **19**, mp 184–186 °C (lit.[3e] mp 184–186 °C).

8-Acetoxy-8-acetyl-7,8,9,10-tetrahydro-6,11-dimethoxy-5,12-naphthacenedione (20). To a stirred suspension of hydroxy ketone **19** (3.00 g) in 100 mL of acetic anhydride was added 0.1 mL of concentrated H_2SO_4. The mixture was heated at 100 °C for 8 h. The solvent residue was crystallized from MeOH–CH_2Cl_2, giving 3.26 g (90%) of **20**, mp 173–175 °C (lit[6]. mp 174–175 °C).

9-Acetoxy-9-acetyl-7-bromo-7,8,9,10-tetrahydro-6,11-diacetoxy-5,12-naphthacenedione (21). A solution of triacetoxy ketone **18** (1.65 g, 3.45 mmoL) and 1,3-dibromo-5,5-dimethylhydrantoin (0.59 g, 2.07 mmoL) in 160 mL of carbon tetrachloride was refluxed (light) under nitrogen. After 3 h an addtional amount of brominating agent (0.1, g, 0.35 mmoL) was added, and reflux continued for 1 h. The solvent was removed and the residue chromatographed (SiO_2, CH_2Cl/EtOAc (5%)) and recrystallized from EtOH–CH_2Cl_2, giving pale yellow needles (1.53 g, 80%) of bromide **21**: mp 216–217 °C; NMR δ 2.13 (s, 3 H, OAc), 2.25 (s, 3 H, CH_3), 2.54 (s, 3 H, ArOAc), 2.57 (s, 3 H, ArOAc), 2.70 (m, 2 H, CH_2), 3.10–3.40 (m, 2 H, benzylic), 5.70 (b, 1 H, H-7), 7.76 (m, 2 H, Ar), 8.16 (m, 2 H, Ar); IR 1780 (ArOAc), 1735 (OAc), 1720 ($COCH_3$), 1685 (quinone), 1580 cm^{-1} (Ar); UV–vis λ_{max} (EtOH) 260 (log ε 4.30), 275 (3.96), 344 nm (3.30); MS, *m/e* 472 (M − $2CH_2CO$, 1), 454 (1), 412 (1), 332 (100), 291 (22), 289 (10). Anal. Calcd for $C_{26}H_{21}O_9Br$: C, 56.03; H, 3.80; Br, 14.34. Found: C, 56.16; H, 3.82; Br, 14.47.

9-Acetoxy-9-acetyl-7-bromo-7,8,9,10-tetrahydro-6,11-dimethoxy-5,12-naphthacenedione (22). A solution of acetoxy ketone **20** (0.3 g, 0.70 mmol) and 1,3-dibromo-5,5-diumethylhydantoin (0.112 g, 0.39 mmoL) in 30 mL of carbon tetrachloride was refluxed for 2 h. The solvent was removed and the residue was chromatographed (SiO_2, CH_2Cl_2–EtOAc (5%)), giving 0.285 g (80%) of bromide **22**: mp 201–204 °C; NMR δ 2.24 (s, 3 H, OAc), 2.37 (s, 3 H, $COCH_3$), 2.80 (m, 2 H, CH_2), 3.10–3.40 (m, 2 H, CH_2), 4.05 (s, 3 H, OCH_3), 4.16 (s, 3 H, OCH_3), 6.60 (d, 1 H, C-7), 7.75 (m, 2 H, Ar), 8.20 (m, 2 H, Ar); IR 1730 (OAc), 1715 (C=O), 1680 (quinone), 1580 cm^{-1} (Ar); UV–vis δ_{max} (CH_3CN) 255 (log ε 4.01), 370 (3.31), 476 (3.29), 508 nm (3.28); MS, *m/e* 500 (M^+, 0.6), 376 (67), 360 (100), 331 (60). Anal. Calcd for $C_{24}H_{21}O_7Br$: C, 57.50; H, 4.22; Br, 15.94. Found: C, 57.21; H, 4.08; Br, 15.68.

7,9-Diacetoxy-9-acetyl-7,8,9,10-tetrahydro-6,11-diacetoxy-5,12-naphthacenedione (28). Method A: Acetates 26 and 27. A mixture of bromide **21** (0.1 g) and excess of silver acetate (0.06 g) in acetic acid was heated at 70 °C for 0.5 h. The reaction mixture was filtered and washed with CH_2Cl_2 and the filtrate concentrated to dryness. The residue was taken up in CH_2Cl_2, washed with aqueous bicarbonate, dried, and concentrated. Preparative TLC (SiO_2, CH_2Cl_2/EtOAc (2%)) gave, in order of elution, 12 mg (13%) of **27**, 23 mg (25%) of **26**, and 26 mg (27%) of **28**.

Acetate 26: mp 219–221 °C (lit.[16a] mp 220–223 °C); NMR δ 2.04 (s, 3 H, OAc), 2.05 (s, 3 H, OAc), 2.25 (s, 3 H, CH_3), 2.52 (s, 3 H, ArOAc), 6.48 (m, $\nu_{1/2}$ = 8 Hz, H-7), 7.80 (m, 2 H, Ar), 8.21 (m, 1 H, Ar), 8.27 (m, 1 H, Ar), 13.53 (s, 1 H, OH); IR 1775 (ArOAc), 1745 (OAc), 1715 ($COCH_3$) 1670 (non-H-bonded quinone), 1630 (H-bonded quinone), 1580 cm^{-1} (Ar); UV–vis λ_{max} (EtOH) 253 (log ε 3.88), 279 (3.53), 401 nm (3.30); MS, *m/e* 452 (M^+ − CH_2CO, 1), 332 (100), 317 (26), 289 (13).

Acetate 27: mp 203–204 °C; NMR δ 2.06 (s, 6 H, 2OAc), 2.17 (s, 3 H, CH_3), 2.52 (s, 3 H, ArOAc), 6.49 (m, $\nu_{1/2}$ = 17 Hz, H-7), 7.80 (m, 2 H, Ar), 8.21 (m, 1 H, Ar), 8.28 (m, 1 H, Ar), 13.57 (s, 1 H, OH); IR 1780 (ArOAc), 1745 (OAc), 1725 ($COCH_3$), 1675 (non-H-bonded quinone), 1635 (H-bonded quinone), 1590 cm^{-1} (Ar); UV–vis λ_{max} (EtOH) 253 (log ε 3.98), 279 (3.65), 401 nm (3.30); MS, *m/e* 452 (M − CH_2CO, 1), 332 (100), 317 (32), 289 (17). Anal. Calcd for $C_{26}H_{22}O_{11}$: C, 63.16; H, 4.48. Found: C, 62.87; H, 4.56.

Method B. Bromide **21** (0.1 g) was treated with silver acetate in acetic acid and worked up as before. The crude reaction mixture was dissolved in acetic anhydride containing one drop of concentrated sulfuric acid and heated at 90 °C for 1.5 h. The solvent was removed, and the residue was dissolved in CH_2Cl_2, washed with $NaHCO_3$, dried, and chromatographed (SiO_2, CH_2Cl_2–EtOAc (10%)), giving **28** (58 mg, 61%) as a mixture (3/2) of isomers: mp 174–175 °C dec; NMR δ 2.04 (s, 6 H, OAc), 2.17 and 2.25 (s, 3 H, CH_3), 2.45, 2.53, and 2.54 (s, 6 H, ArOAc), 6.34 and 6.52 (b, 1 H, H-7), 7.75 (m, 2 H, Ar), 8.15 (m, 2 H, Ar); IR 1780 (ArOAc), 1745 (OAc), 1725 ($COCH_3$), 1675 (non-H-bonded quinone), 1585 cm^{-1} (Ar); UV–vis λ_{max} (EtOH) 256 (log ε 4.32), 275 (4.03), 339 nm (3.29); MS, *m/e* 494 (M − CH_2CO, 1), 452 (4), 392 (3), 332 (100), 317 (13), 307 (12). Anal. Calcd for $C_{28}H_{24}O_{11}$: C, 62.69; H, 4.51. Found: C, 62.42; H, 4.60.

(±)-Demethoxydaunomycinone (24) and (±)-4-Demethoxy-7-epidaunomycinone (25). Method A. To 0.4 g (0.72 mmol) of bromide **21** in trifluoroacetic acid (10 mL) was added a solution of silver trifluoroacetate (0.4 g, 1.81 mmol) in 5 mL of trifluoroacetic acid. The mixture was stirred at room temperature for 2 h. After the solvent was removed, the residue was taken up with CH_2Cl_2, separated from the silver salt by filtration, and washed with H_2O. The solvent was evaporated, the residue was dissolved in a mixture of 15 mL of THF and 15 mL of NaOH (0.5 N) and was stirred under nitrogen at room temperature for 2 h. The blue solution was diluted with H_2O, acidified with HCl (12%) until the color changed to red, extracted with CH_2Cl_2, dried, and concentrated. The residue was chromatographed (SiO_2, CH_2Cl_2–EtOH (1%)), giving 0.107 g (41%) of **24**: mp 173–175 °C dec (lit.[26,27] mp 167–170 °C); NMR δ 2.19 (dd, 1 H, *J* = 14, 5 Hz), 2.35 (m, 1 H), 2.44 (s, 3 H), 2.97 (d, 1 H, *J* = 19 Hz), 3.20 (dd, 1 H, *J* = 19, 2 Hz), 3.81 (d, 1 H, *J* = 6 Hz, 9-OH), 4.56 (s, 1 H, 7-OH), 5.32 (m, 1 H, $\nu_{1/2}$: 8 Hz, H-7), 7.84 (m, 2 H), 8.34 (m, 2 H), 13.31 (s, 1 H, phenolic OH), 13.59 (s, 1 H, phenolic OH); IR 3370 (b, OH), 1710 ($COCH_3$), 1630, 1585 cm^{-1}; MS, *m/e* 368 (M^+, 2), 332 (100), 317 (45) 289 (15). Continued elution afforded 0.053 g (20%) of **25**: mp 203–204 °C (lit.[26] mp 205 °C); NMR δ 2.14–2.37 (m, 2 H, CH_2), 2.41 (s, 3 H, $COCH_3$), 2.95 (d, 1 H, *J* = 18 Hz, H-10), 3.10 (d, 1 H, *J* = 18 Hz, H-10), 3.88 (s, 1 H, OH), 4.27 (s, 1 H, OH), 5.41 (m, 1 H, $\nu_{1/2}$ = 18 Hz, H-7), 7.85 (m, 2 H), 8.35 (m, 2 H), 13.32 (s, 1 H, phenolic OH), 13.94 (s, 1 H, phenolic OH); IR 3330 (b, OH), 1710, 1630, 1585 cm^{-1}; MS, *m/e* 368 (M^+, 15), 350 (18), 332 (63), 317 (29), 309 (41), 307 (100). Both compounds were identical (TLC, MS, NMR, IR) with authentic samples of **24** and **25**.[21]

Method B. To a cooled solution (0–5 °C) of bromide **21** (0.37 g, 0.66 mmoL) in THF (50 mL) was slowly added a solution of sodium hydroxide (0.19 g, 4.75 mmoL) in 50 mL of H_2O. The mixture was stirred at this temperature under nitrogen for 2 h and then at room temperature for another 12 h. Acidification, extraction with CH_2Cl_2, and evaporation gave 0.24 g of crude material. The above mixture was dissolved in TFA (10 mL) and stirred at room temperature for 2 h. The TFA was evap-

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orated and the residue was dissolved in a mixture of MeOH (15 mL), THF (10 mL), and aqueous sodium bicarbonate 5% (10 mL). After the mixture was stirred at room temperature for 15 min, the product was extracted with CH_2Cl_2, dried, and concentrated. Chromatography of the residue (SiO_2, CH_2Cl_2) gave 0.062 g (29%) of the bis(anhydro) derivative **29**: mp 250–252 °C; NMR δ 2.78 (s, 3 H, CH_3), 7.84 (m, 2 H, Ar), 8.32 (dd, 1 H, J = 8, 1.5 Hz, H-8), 8.46 (m, 2 H, Ar), 8.54 (d, 1 H, J = 8 Hz, H-7), 8.99 (dd, 1 H, J = 1.5 Hz, H-10), 14.93 (s, 1 H, OH), 15.08 (s, 1 H, OH); IR 1690 ($COCH_3$), 1630 (H-bonded quinone), 1590 cm^{-1} (Ar); UV–vis λ_{max} (CH_3CN) 267 (log ϵ 3.57), 4.54 (sh, 2.72), 478 (2.87), 510 nm (2.77); MS, m/e 332 (M, 100), 289 (22), 261 (15), 233 (19); anal. calcd for $C_{20}H_{12}O_5$; 332.0681; found, 332.0682.

Continued elution with CH_2Cl_2–EtOH (1%) gave 0.115 g (48%) of **24** and 0.022 g (9%) of **25**, identical (TLC, MS, NMR) with samples obtained in method A.

Method C. A sample of tetraacetate **28** (20 mg) was hydrolyzed in 10 mL of MeOH–H_2O (4:2) with 0.5 mL of HCl (12%). The resulting solution was refluxed under nitrogen for 3 days. The mixture was poured into H_2O and extracted with CH_2Cl_2. The organic phase was dried and concentrated, giving 11.3 mg (85%) of a crude mixture of **24** and **25** (2:1, respectively), containing less than 3% of aromatic **29**. Epimerization as before gave 44% of (±)-4-demethoxydaunomycinone (**24**) and 9% of the 7-epi isomer (**25**), after chromatography.

Method D. To 0.10 g of bromide **22** in 5 mL of trifluoroacetic acid was added 0.130 g of silver trifluoroacetate. The mixture was stirred for 2 h at room temperature. The solvent was removed and the residue was dissolved in CH_2Cl_2 and filtered. To the solution was added 0.20 g of $AlCl_3$. This mixture was stirred for 15 min at room temperature; at this point the methylene chloride was shaken with dilute HCl, and the layers were separated and dried. The methylene chloride was removed in vacuo and the residue was dissolved in 20 mL of THF and to this was added 5 mL of 10% NaOH. This solution was stirred for 2 h; at this point the solution was neutralized with 10% HCl and extracted with methylene chloride. The layers were separated and the methylene chloride was removed in vacuo. Epimerization of the residue was accomplished with 10 mL of trifluoroacetic acid and by stirring for 2 h at room temperature. The solvent was removed in vacuo and the residue was chromatographed (SiO_2, CH_2Cl_2/MeOH(3%)), giving 5.7 mg (8%) of the epi isomer **25** and 28.7 mg (40%) of the cis isomer **24**.

Acknowledgment. We thank Adria Laboratories, Columbus, OH, for a grant in support for this work.

Registry No. 4, 77422-62-9; **5**, 84498-97-5; **6**, 76811-56-8; **7** (isomer 1), 84498-98-6; **7** (isomer 2), 84498-99-7; *cis*-**10**, 84499-00-3; *trans*-**10**, 84499-01-4; **11**, 84499-02-5; *cis*-**12**, 84499-03-6; *trans*-**12**, 84499-04-7; (±)-**16**, 65529-77-3; **16**, 63229-48-1; **16** (hydrazone, isomer 1), 84499-05-8; **16** (hydrazone, isomer 2), 84499-06-9; **17**, 84198-22-1; **18**, 69813-88-3; **19**, 33628-86-3; **20**, 84499-07-0; **21**, 84499-08-1; **22**, 84499-09-2; **24**, 58924-49-5; **25**, 65877-42-1; **26**, 70071-85-1; **27**, 71571-55-6; **28** (isomer 1), 84499-10-5; **28** (isomer 2), 84499-11-6; **29**, 84499-12-7.

Cyclic Phosphonic–Carboxylic Imides and Anhydrides as Reactive Intermediates. 1. Rearrangement and Solvolysis of *N*-(Amino(methyl)phosphinyl)-L-phenylalanine Derivatives

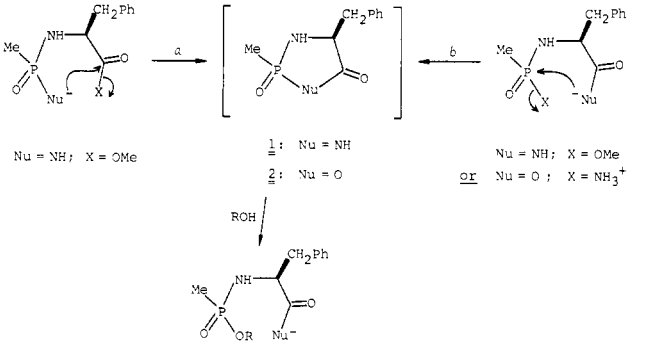
Neil E. Jacobsen and Paul A. Bartlett*

Contribution from the Department of Chemistry, University of California, Berkeley, California 94720. *Received August 5, 1982*

Abstract: Structural, kinetic, and stereochemical evidence indicates the involvement of cyclic intermediates of the structure Me-P(O)-L-Phe-X, **1** (X = NH) and **2** (X = O), in the anomalous reactions of derivatives of *N*-(amino(methyl)phosphinyl)-L-phenylalanine. Cyclization of Me-PO(NH_2)-L-Phe-OMe (**7**) and Me-PO(OMe)-L-Phe-NH_2 (**12**) gives **1**, while cyclization of Me-PO(NH_2)-L-Phe (**10**) gives **2**. The transient intermediates **1** and **2** are not observed, but rapidly undergo ring opening at phosphorus by a solvent molecule. Evidence for the intermediacy of **1** and **2** includes the transfer of NH_2 from phosphorus to the phenylalanine carbonyl in the base-catalyzed solvolysis of **7**, large rate accelerations in the base-catalyzed solvolysis of **12** and the acid-catalyzed solvolysis of **10**, and the stereochemical outcome of the latter reaction: the configuration at phosphorus is retained, as predicted by a cyclization–ring opening mechanism. The S_P diastereomer of **2**, in which the methyl and benzyl groups are cis related in the ring, is formed 2–3 times faster than the R_P isomer.

In connection with our investigations of phosphonamidate dipeptide analogues as inhibitors of carboxypeptidase A,[1] we required the phosphonic diamide **10**. During the course of our synthetic work, we observed a number of anomalous reactions, for example the extreme hydrolytic sensitivity of **10** in comparison to the carboxylic ester derivative **7**, and the ready transformation of **7** into the carboxamide **9** under alkaline conditions (see Scheme III). These reactions appeared to involve transient intermediates **1** and **2** (Scheme I). Such intermediates arise either by cyclization of a phosphorus-bound nucleophile on the acyl carbon (path a) or by cyclization of a carbon-bound nucleophile on the phosphorus center (path b). In hydroxylic solvents, the intermediates **1** and **2** undergo rapid cleavage, exclusively at phosphorus, to give overall nucleophile transfer and solvolysis (path a) or catalyzed solvolysis (path b).

Scheme I



A number of previous studies have implicated five-membered ring phosphoric–carboxylic and phosphonic–carboxylic anhydride

(1) Jacobsen, N. E.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 654.

0002-7863/83/1505-1613$01.50/0