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THE SYNTHESIS OF (±) α-CITROMYCINONE VIA A 1,4-DIPOLE-METALLATED *p*-QUINOL STRATEGY

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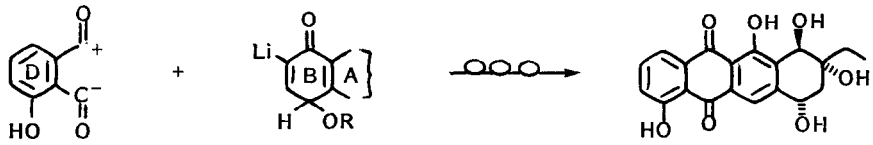
Abstract: *The synthesis of the compound having the structure assigned to α-citromycinone has been completed in 4% overall yield from 2-ethyl-5,8-dimethoxy-7-bromo-1-tetralone.*

The last several years have witnessed an intense interest in the synthesis of the aglycon portion of anthracycline antibiotics.[1] One of the rarest anthracyclinones is α-citromycinone which was obtained in only 0.1% yield from the fermentation broth of *Streptomyces purpurascens*.[2] Aside from the academic interest associated with a regiospecific synthesis of α-citromycinone, there is also the proposal that 6-deoxyanthracyclinones may show reduced cardiotoxicity.[3]

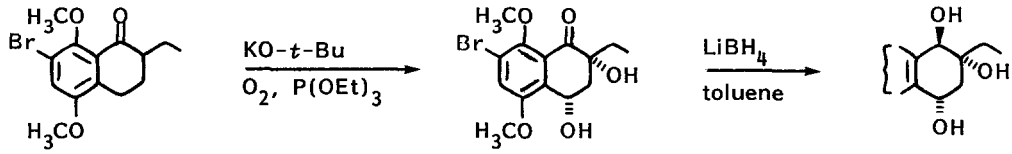
1, α-citromycinone 2

One approach to the synthesis of 1 would involve preparation of 2 followed by introduction of the C_7- and C_{10}-hydroxyl groups. While such a route would almost certainly not be stereospecific, this point is inconsequential since a variety of procedures proved unsuccessful in converting 2 to 1.[4] This lack of an efficient 2 → 1 conversion has apparently frustrated other attempted syntheses of α-citromycinone.[5,6] An alternative approach is the coupling of a 1,4-dipole equivalent with a fully functionalized metallated *p*-quinol synthon as outlined in Scheme I.[7] We report here the total synthesis of the compound having the structure assigned as (±) α-citromycinone[8] using the strategy of Scheme I.

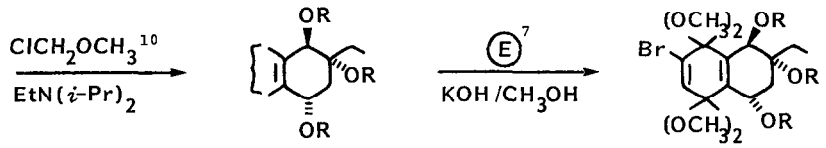
Scheme I. 1,4-Dipole-Metallated *p*-Quinol Strategy to α-Citromycinone



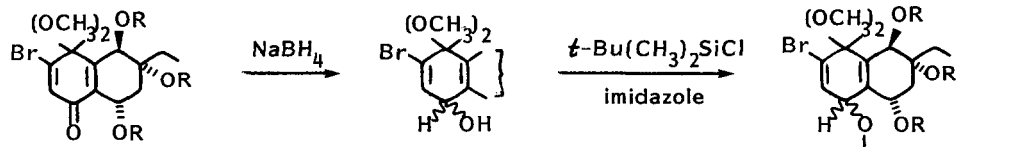
The synthesis of the AB-ring segment which would serve as a metallated *p*-quinol equivalent is outlined below. The triol 5, available from the tetralone 3,[9] was protected as its trimethoxymethyl ether derivative and anodically oxidized in a divided cell to give 7. Monohydrolysis of



3 4 (50-60%) 5 (76%)



6 (65%, oil) 7 (87%, oil)

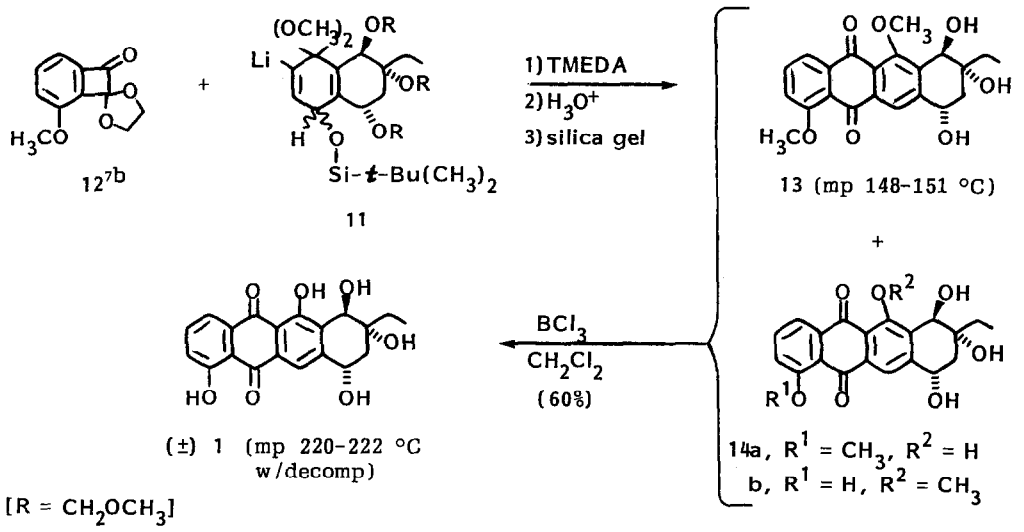


8 (71%, mp 100-101.5 °C) 9 (98%, oil) 10 (92%)

[R = CH_2OCH_3]

the crude electrolysis product gave the crystalline monoketal 8. Reduction of 8 gave 9 as a 2:1 epimeric mixture which was directly converted to its *t*-butyldimethylsilyl derivative. Trituration of crude 10 with ether gave the epimeric silyl ethers as a white solid.

There remained to be accomplished the bromine-lithium exchange chemistry and the reaction of the resulting lithium compound with the 1,4-dipole equivalent 12. Reaction of 10 with two equivalents of *t*-butyllithium at -78 °C for 25 minutes gave nearly complete bromine-lithium exchange with no aromatization of 10. Addition of TMEDA (6.5 equivalents) to the organolithium species 11 was followed by addition of 12 (2 equivalents). The reaction mixture was stirred at -78 °C for 5 minutes and at -61 °C for 25 minutes, warmed to room temperature, and then heated at reflux for 3 hours. The crude product was subjected to acid hydrolysis,[12] and the product mixture was chromatographed on silica gel. There was obtained a mixture of two yellow products 13 and 14, difficultly separable by chromatography, in combined yields of 37 and 43% (two runs). The major compound from the mixture was obtained pure, and spectroscopic data established its structure as 13.[13] No further attempts were made to purify the minor product in this mixture when it was found that the 13/14 mixture reacted with boron trichloride to give 1. The ^{1}H NMR



spectrum of the 13/14 mixture suggested one of the compounds had lost a methyl group during the reaction sequence; thus, the second component in the mixture is probably 14a or 14b.

Since no authentic sample of 1 is available, the assignment of 1 as (±) α-citromycinone rests with comparison of the data in Table 1 and the ^1H NMR spectra in Figure 1. The nearly identical pattern in the high-field region of 1 with that reported for α_2-rhodomycinone[2] leaves no doubt that 1 has the required A-ring stereochemistry as shown.

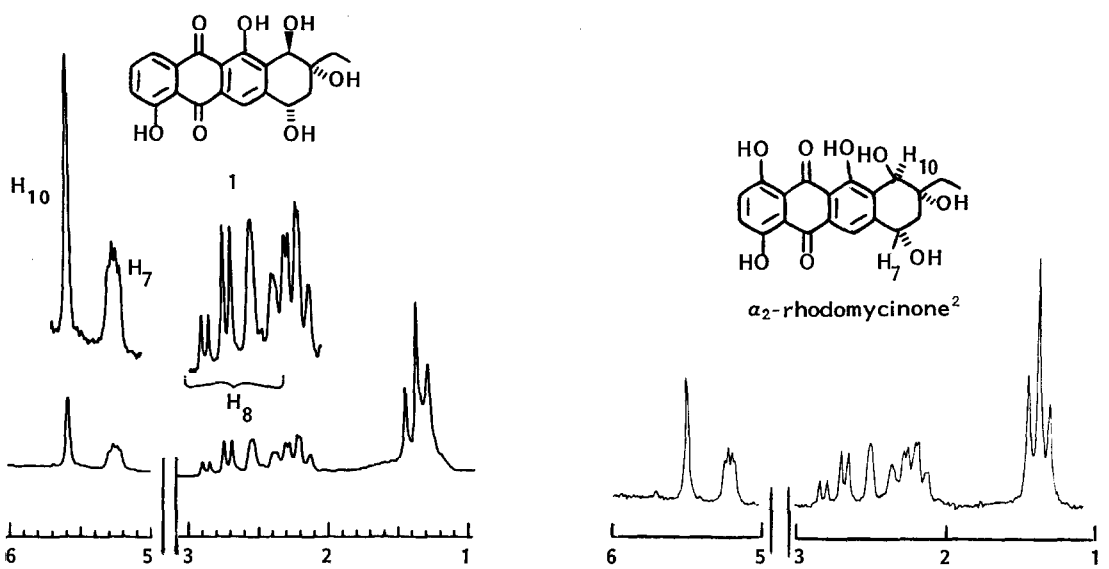


Figure 1. Comparison of ^1H NMR (C_5D_5N) spectra of 1 and α_2-rhodomycinone

Table 1. Comparison of Properties of Synthetic and Natural α-Citromycinone

property	synthetic 1	α-citromycinone
λ_{max} (cyclohexane)	417 nm (log ε 3.92) 435 nm (log ε 3.92)	418 nm (log ε 4.04) 436 nm (log ε 4.04)
IR (KBr)	3375, 1625, 1600 cm^{-1}	3370, 1622, 1598 cm^{-1}
mass spectrum (70 ev)	prominent peaks at M^+-18, M^+-36, M^+-52, M^+-72	prominent peaks at M^+-18, M^+-36, M^+-72

In summary, α-citromycinone has been prepared in nine steps from 3 in ∿4% yield using a 1,4-dipole-metallated *p*-quinol strategy. This same strategy should afford a general route to other 6-deoxyanthracyclinones by using modified AB- and CD-ring segments.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for financial support.

References and Notes

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(7) For an analogous strategy to rhodomycinones, see: (a) Jackson, D. K.; Narasimhan, L.; Swenton, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 3989. (b) Swenton, J. S.; Anderson, D. K.; Jackson, D. K.; Narasimhan, L. *J. Org. Chem.* **1981**, *46*, 4825.

(8) Professor Bröckmann has informed us that an authentic sample of α-citromycinone is not available.

(9) Coburn, C. E.; Anderson, D. K.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1982**, 987.

(10) Greene, T. W. "Protective Groups in Organic Synthesis;" J. Wiley and Sons, New York, 1981, p. 296.

(11) Henton, D. R.; Anderson, D. K.; Manning, M. J.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 3422. The regiochemistry of 8 was established as outlined in this reference.

(12) A mixture of tetrahydrofuran (30 mL)/water (13 mL) and concentrated hydrochloric acid (5 mL) at room temperature was used for hydrolyzing a run from 0.5 g of 10 (60 h reaction time).

(13) ^{1}H NMR (90 MHz, $CDCl_3$) δ 8.15 (s, 1 H), 7.81 (dd, *J* = 7.8, 1.5 Hz, 1 H), 7.63, (t, *J* = 7.8 Hz, 1 H), 7.22 (dd, *J* = 7.8, 1.5 Hz, 1 H), 4.85 (unresolved m, collapses to t with D_2O, *J* = 3.2 Hz, 1 H), 4.75 (s, 1 H), 3.95 (s, 6 H), 3.05 (br s, OH, 1 H), 2.54 (unresolved d, OH, 1H), 2.12 (d, separation ∿3.2 Hz, 2 H), 1.78 (q, *J* = 7.6 Hz, 2 H), 1.05 (t, *J* = 7.6 Hz, 3 H).

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