Tetrahedron Letters, Vol.22, No.18, pp 1667 - 1670, 1981
Printed in Great Britain

0040-4039/81/181667-04$02.00/0

A REGIOSPECIFIC APPROACH TO 6-DEOXYANTHRACYCLINONES; THE STRUCTURE OF γ-CITROMYCINONE

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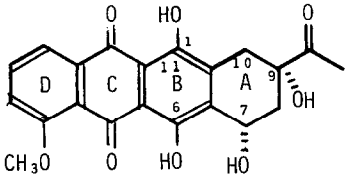
ABSTRACT: The known tetralone 5 has been regiospecifically converted in 10 steps (11% yield) to the 6-deoxy tetracyclic ketone 15. Our sequence includes a novel one-step oxidation of 5 to naphthaldehyde 6, and an unusual enone to phenol isomerization (12 → 14). Although C-7 functionalization of carbinol 17 failed, olefin 18 was converted to diol 4. The properties of 4 did not agree with those reported for γ-citromycinone, suggesting that the latter has the isomeric structure 3.

Recent advances in the regiospecific synthesis of anthracyclinones have provided several viable routes to compounds bearing the 6,11-dihydroxylated B-ring characteristic of daunomycinone (1).[1] No comparable methodology has been developed for synthesis of 6-deoxyanthracyclinones represented by the known α-citromycinone (2) and by the rare aglycone γ-citromycinone, for which the two alternative structures 3 and 4 have been postulated.[2] We describe here an unusual and completely regiospecific route to the 6-deoxy ketone 15 and subsequent chemistry which permits a structural assignment for γ-citromycinone.[3]



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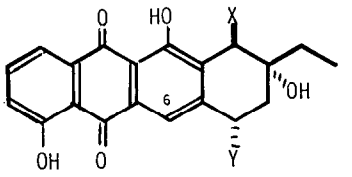
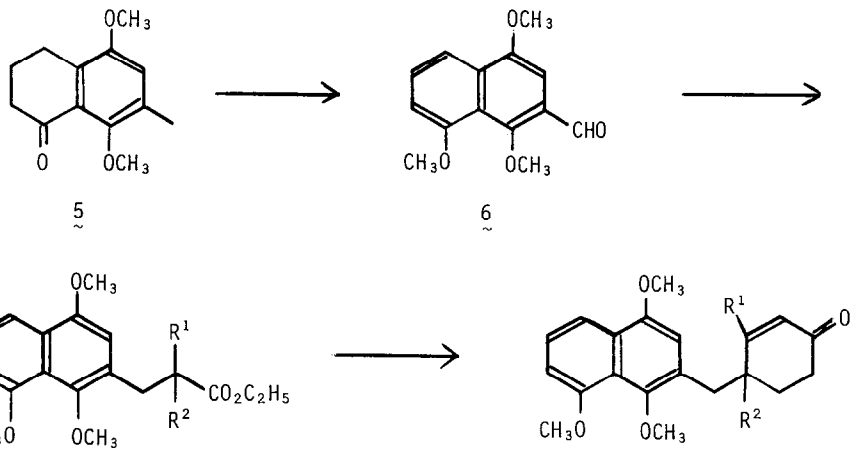


2 X = Y = OH
3 X = H, Y = OH
4 X = OH, Y = H

The key C—D bicyclic synthon 6 for our synthesis was prepared by a remarkable one-pot reaction. This transformed the known tetralone 5[4] by oxidation with 3.2 eqt of DDQ and 1 eqt of $HC(OCH_3)_3$ in CH_3OH (reflux, 24 h) directly to naphthaldehyde 6, mp 89-90°, in 65% yield.[5] Emmons condensation (1.2 eqt $(EtO)_2POCH_2CO_2Et$, 1.5 eqt NaH, C_6H_6, rt, 4 h)[6] and subsequent hydrogenation (H_2, 5% Pd-C, EtOH, rt) gave 92% of the ester 7, mp 62-64°, which on Claisen acylation (1.0 eqt Et_2 oxalate, 2.0 eqt NaH, C_6H_6, 55°, 20 h)[7] gave 68% of the ketodiester 8. This was reacted with methyl vinyl ketone (cat Et_3N, 1:1 EtOH-C_6H_6, reflux, 20 h) to yield 80% of the Michael adduct 9, mp 110-111°. The latter was cyclized by way of the *in situ* generated enamine (xs pyrrolidine, C_6H_6, cat AcOH, reflux, 5 h)[8] to yield exclusively the tricyclic ketodiester 10, mp 107-109°, in 87% yield. Alkaline hydrolysis (5 eqt KOH, EtOH, reflux 24 h) gave the ketoacid 11, mp 215-217° dec, in 95% yield.



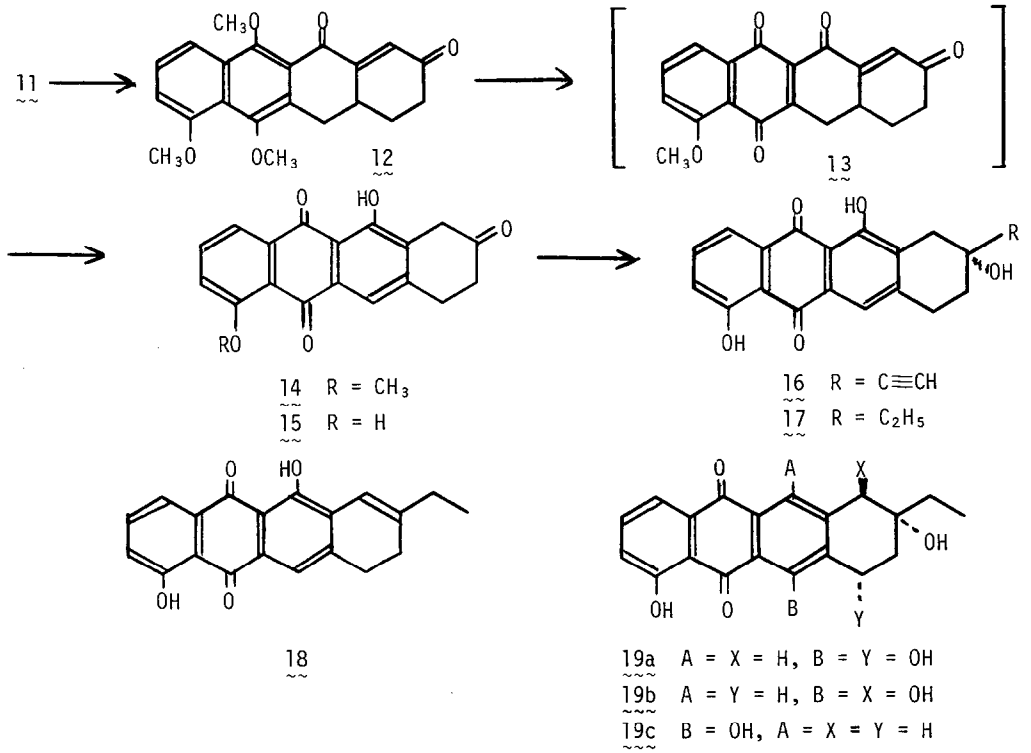
5 6

7 $R^1 = R^2 = H$
8 $R^1 = COCO_2C_2H_5$, $R^2 = H$
9 $R^1 = COCO_2C_2H_5$, $R^2 = CH_2CH_2COOCH_3$

10 $R^1 = R^2 = CO_2C_2H_5$
11 $R^1 = CO_2H$, $R^2 = H$

Cyclodehydration of ketoacid 11 (2:1 TFA-TFAA, reflux, 2h) gave the tetracyclic enedione 12, mp 204-206°, in 63% yield [^{1}H-NMR: δ7.95 (1H, d, J = 8 Hz), 7.46 (1H, t, J = 8 Hz), 7.05 (1H, d, J = 8 Hz), 6.96 (1H, d, J = 3 Hz), 4.07 (s, 6H), 3.83 (s, 3H), 1.5-3.5 (7H, m)]. Argentic oxide oxidation (4 eqt AgO, Me_2CO, HNO_3, rt, 3 min)[9] produced an intermediate tetracyclic naphthoquinone (13, λ_{max} 222, 264, 354 nm). In a critical step, the crude quinone 13 underwent prototropic isomerization at rt in acetone in the presence of a few drops of conc HCl to give 93% of the orange-yellow quinone 14, mp 248-250° [^{1}H-NMR: δ12.80 (1H, s), 7.88 (1H, d, J = 8 Hz), 7.62 (1H, t, J = 8 Hz), 7.54 (1H, s), 7.26 (1H, d, J = 8 Hz), 4.06 (3H, s), 3.60 (2H, s), 3.18 (2H, t, J = 7 Hz), 2.59 (2H, t, J = 7 Hz)].[10] $AlCl_3$ demethylation (8 eqt $AlCl_3$, CH_2Cl_2, rt, 18 h) converted quinone 14 in 72% yield to the desired 6-deoxy tetracyclic ketone 15, mp 249-251°, [^{1}H-NMR: δ13.01 (1H, s), 12.64 (1H, s), 7.7 (3H, m), 7.29 (1H, d, J = 8 Hz), 3.68 (2H, s), 3.05 (2H, t, J = 7 Hz), 2.62 (2H, t, J = 7 Hz)].

Ketone 15 was efficiently ethynylated (xs HC≡CH, EtMgBr, THF, 0°) to give 67% of the ethynyl carbinol 16, which on diimide reduction (xs KO_2CNNCO_2K, pyridine, AcOH, 55°)[11] gave 66% of the ethyl carbinol 17, mp 214-216°. In contrast to our results in the rhodomycinone series,[11] all attempts to introduce C-7 oxygen by free radical bromination of 17 (or by other oxidants) failed to yield any of the desired diol 3. Aside from starting material and aromatized products, the only new polar material observed was the diol 4, apparently arising from the bromination of the hindered but peri-activated C-10 position. The latter diol was independently synthesized from carbinol 17 by dehydration (6 eqt $AlCl_3$, CH_2Cl_2, rt, 18 h) to 18, mp 174-176°, followed by epoxidation (6 eqt MCPBA, CH_2Cl_2, rt) and subsequent trans[11,12] cleavage with base (0.3 M NaOH, 1:1 H_2O-THF, rt, 18 h) to produce 63% of diol 4, mp 208-209° [^{1}H-NMR: δ13.50 (1H, s), 12.60 (1H, s), 7.6-7.9 (3H, m), 7.32 (1H, d, J = 8 Hz), 4.82 (1H, s), 3.81 (1H, s), 3.10 (1H, m), 2.80 (1H, s), 2.8 (1H, m), 2.2 (1H, m), 1.6 (3H, m), 1.02 (1H, t, J = 7 Hz)].



Although the mp of racemic diol 4 was close to that reported for γ-citromycinone (mp 207° dec), no comparison sample of the natural aglycone was available, and no NMR spectrum had been obtained by Brockmann and Niemeyer. However, substantial discrepancies have been found between the mass spectrum and the stability to catalytic hydrogenation of our synthetic diol 4 and the properties reported for γ-citromycinone. As shown in Table I, the reported spectrum of γ-citromycinone exhibited a small molecular ion at m/e = 354 (14% of base), a large retro Diels-Alder fragment at m/e = 282 (36%) and a base peak at m/e = 280. In contrast, synthetic diol 4 exhibited a base peak at m/e = 279, a large molecular ion at m/e = 354 (45%), and only a weak retro Diels-Alder fragment at m/e = 282 (14%). This pattern for 4 was essentially independent of ionizing voltage and probe temperature.

TABLE I - MASS SPECTRA OF SYNTHETIC DIOL 4 VS. γ-CITROMYCINONE[13]

m/e	Diol 4	γ-Citromycinone
354 (M^{+})	45	14
336	46	28
318	32	20
307	50	6
282 (retro-DA)	14	36
280	30	100
279	100	18
254	57	20

Brockmann and Niemeyer showed that catalytic reduction of α-citromycinone (2) over 5% Pd-$BaSO_4$ (50% triethanolamine in EtOH, rt, 1 h) produced γ-citromycinone. They postulated that a benzylic hydroxyl adjacent to a peri phenolic hydroxyl undergoes ready hydrogenolysis,

whereas one without the peri phenol is stable. On this basis they suggested that hydrogenolysis of α-citromycinone cleaves the C-10 hydroxyl, leading to probable structure 3 for γ-citromycinone. In accord with their postulate, we find that decarbomethoxyaklavinone 19a is readily reduced under Brockmann-Niemeyer conditions to 19c, whereas synthetic model 19b is inert. Moreover, we find that our synthetic diol 4 is smoothly reduced under the above conditions to the ethyl carbinol 17.

We conclude that the properties reported for γ-citromycinone are not in accord with those observed for diol 4, and that the natural aglycone almost certainly has the structure 3. Finally, we find that synthetic access to the 6-deoxy ketone 15 does not provide facile entry to α-citromycinone (or to 6-deoxydaunomycinone) because the absence of a C-6 phenolic hydroxyl deactivates the C-7 benzylic position for the requisite homolytic functionalization.

Acknowledgments: We are grateful to Professor Hans Brockmann for furnishing us unpublished spectra and the J. Niemeyer dissertation, to Professor Federico Arcamone for a reference sample of decarbomethoxyaklavinone, and to J. P. Rizzi for providing key intermediates. Partial support of this research by grant CA 11326 from the National Cancer Institute (USPHS). by a Sherman Clarke Fellowship (to T.P.D.), and by a NATO travel grant (to J.-P.G.) are acknowledged with thanks.

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(Received in USA 21 January 1981)