Tetrahedron Letters, Vol.22, No.19, pp 1779 - 1782, 1981
Printed in Great Britain

0040-4039/81/191779-04$02.00/0

A REGIOSPECIFIC SYNTHESIS OF (±)-DECARBOMETHOXYAKLAVINONE

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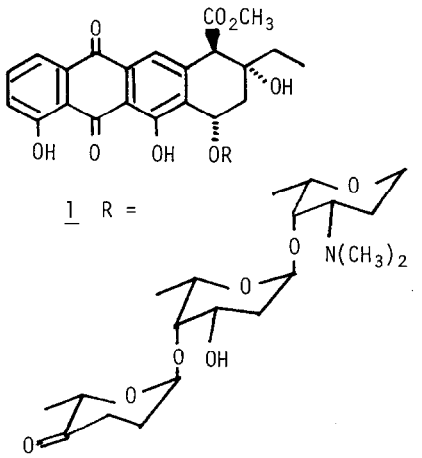
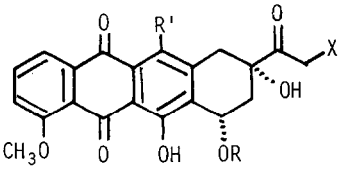
ABSTRACT: Condensation of the dilithio derivative of 3-methoxybenzanilide with the bicyclic ketoaldehyde 12 leads to a convergent and 100% regiospecific synthesis of (±)-decarbomethoxyaklavinone (19).

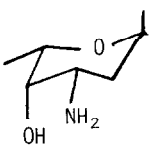
Aclacinomycin A (1)[1] is a relatively new anthracycline antibiotic which appears to have good antineoplastic activity but reduced toxicity relative to adriamycin (2). The corresponding aglycone, aklavinone (3), and the recently described 11-deoxydaunomycinone (4)[2] are examples of anthracyclinones bearing hydroxyl at C-6 but not at C-11 of the anthracyclinone framework. To our knowledge, no synthesis of such C-11 deoxyanthracyclinones has been described in the literature. We now report a facile, convergent and 100% regiospecific strategy which may offer a general solution to this important challenge.



1 R =

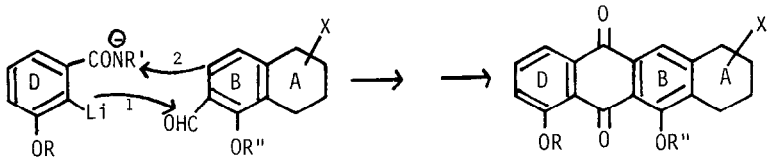
3 R = H



2 X = OH, R = 
R' = OH

4 X = H, R = H, R' = H

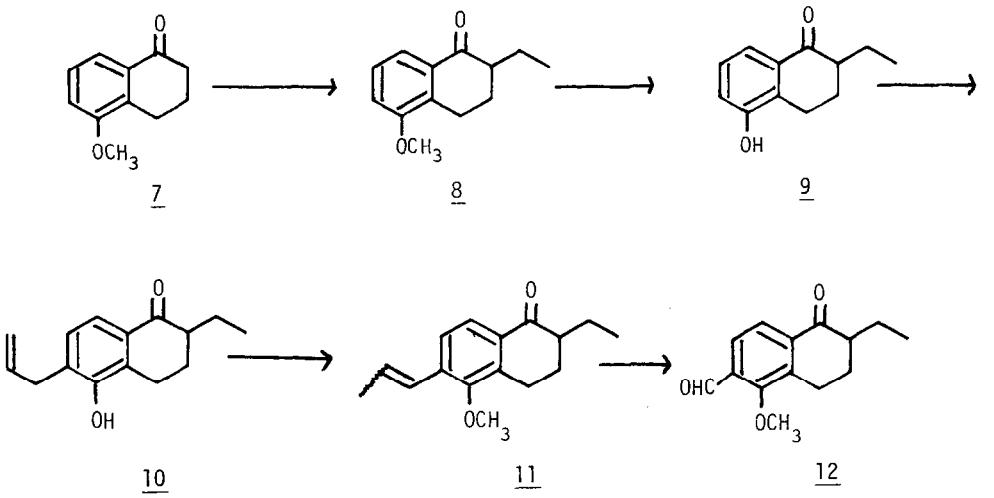
Our synthetic strategy employs the condensation of a preformed bicyclic A/B-ring aldehyde (6) with a nucleophilic D-ring carboxamide (5), with stepwise bond formation as in the equation below.



5 6

We illustrate this strategy for the simple case leading to the total synthesis of racemic decarbomethoxyaklavinone, 19. For this target, our AB synthon 12 was prepared from 5-methoxytetralone (7) by the sequence depicted in Scheme I.

SCHEME I



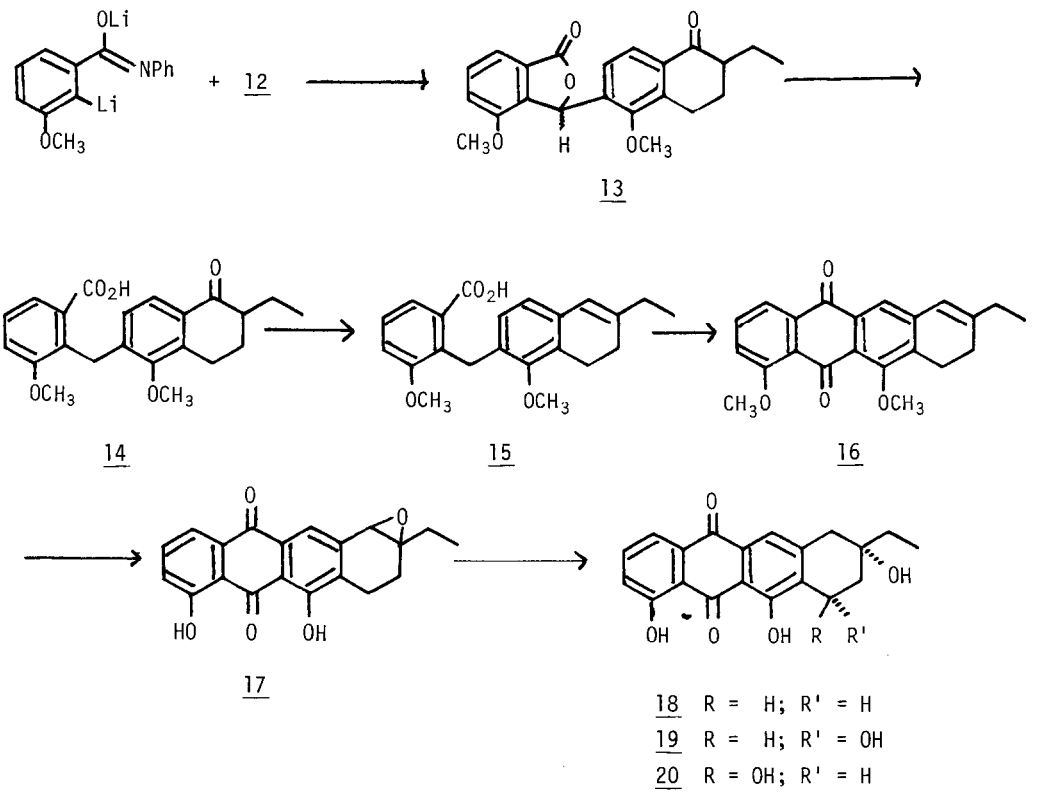
Monoalkylation of tetralone 7 at C-2 was not as facile as expected. Under most conditions severe mixtures of mono- and diethyl derivatives were produced, along with starting 7. This problem could be surmounted by reaction of the lithium enolate of 7 in THF with one equivalent of triethanolamine borate in DMSO[3] (25°, 4 hr) followed by ethyl iodide to give an 80% yield of tetralone 8 (oil, tosylhydrazone mp 177-178°) and 14% starting 7.

Direct electrophilic formylation of 8 using Cl_2CHOCH_3 and $SnCl_4$ gave almost entirely the 8-formyl derivative. Therefore, methoxyketone 8 was demethylated[4] (NaSEt, DMF, reflux, 2 hr) to phenol 9 (mp 127-129°) in 96% yield. Allylation of this phenol with allyl bromide (K_2CO_3, acetone, reflux, 6 hr) followed by Claisen rearrangement in $PhNMe_2$ at 200° for 24 hr gave 87% of the C-allyl phenol 10 (mp 76-78°). Remethylation (MeI, K_2CO_3, acetone, reflux, 6 hr) followed by isomerization with t-BuOK (t-BuOH, reflux, 5 hr) gave tetralone 11 (mp 69-70°) in 93% yield. Ozonolysis of 11 (CH_2Cl_2, -78°, Me_2S) gave the desired bicyclic aldehyde 12, (mp 99-100°) in 80% yield [nmr in $CDCl_3$: δ10.56 (s, 1H); 8.00 (d, J = 8, 1H); 7.84 (d, J = 8, 1H); 4.00 (s, 3H); 3.42-1.39 (m, 7H); 1.02 (t, J = 8, 3H)].

It had been previously established that various 3-methoxybenzamides can be lithiated regiospecifically at position 2, and that these lithium derivatives can be condensed with benzaldehydes in respectable yields.[5] We chose to use 3-methoxybenzanilide because of the higher yields claimed for such substrates.[5a] As summarized in Scheme II, the dilithio derivative of

3-methoxybenzanilide was prepared (2 BuLi, TMEDA, THF, -78° to -20°, 4 hr) and to it was added a THF solution of the aldehyde 12 at -78°. After the reaction was allowed to reach room temperature overnight there was obtained 70% of phthalide 13 as a 1:1 mixture of diastereomers, mp 160-166°. Reduction of phthalide 13 with zinc dust in aqueous NaOH and pyridine[6] (reflux, 24 hr) gave ketoacid 14, mp 168-170°, in 95% yield.

SCHEME II



Direct cyclodehydration of ketoacid 14 to form the C-ring was unsuccessful. As an alternative, $NaBH_4$ reduction of ketoacid 14 (EtOH, rt, 24 hr) followed by dehydration of the crude alcohol (cat. pTSA, C_6H_6, reflux, 2 hr) gave the olefinic acid 15 as a white foam in 96% yield. Ring closure ($CF_3CO_2H/(CF_3CO)_2O$, CH_2Cl_2, rt, 2 hr) gave the corresponding anthrone which was air oxidized (K_2CO_3, CH_3OH, rt, 4 hr) to yield, after Si gel chromatography, 48% of the yellow quinone 16. Demethylation ($AlCl_3$, CH_2Cl_2, rt, 4 hr) followed by epoxidation (m-CPBA, CH_2Cl_2, rt, 6 hr) gave epoxyquinone 17, mp 173-175°, in 65% yield.

Hydrogenolysis of the epoxide function[7] of 17 (H_2, Pd-$BaSO_4$, 1:1 EtOH-$N(CH_2CH_2OH)_3$, rt, 3 hr) gave carbinol 18, mp 184-186°, in quantitative yield. Introduction of the C-7 oxygen was achieved by homolytic bromination

of 18 (Br_2, AIBN, CCl_4, reflux, 1 hr) followed by solvolysis in 1:1 aq. $NaHCO_3$-THF (rt, 30 min). This gave as kinetic products decarbomethoxyaklavinone 19 (25%) and its pseudo-equatorial C-7 epimer 20 (5%). Synthetic 19 (mp 198-200° dec) was compared with authentic 19 (mp 192-194° dec; mix mp = 178-182° dec) obtained from natural aklavinone and exhibited identical mass spectrum [$\frac{m}{e}$ 354, 336, 318, (100%), 307, 303, 280], nmr in $CDCl_3$ [δ12.70 (s, 1H); 12.04 (s, 1H); 7.84 (d, J = 8, 1H); 7.69 (t, J = 8, 1H); 7.65 (s, 1H); 7.31 (d, J = 8, 1H); 5.30 (m, 1H, $\nu_{\frac{1}{2}} \simeq 8$ Hz); 3.53 (d, J = 6, 1H); 3.25 (s, 1H); 3.10 and 2.81 (AB quartet, J = 20, 2H); 2.45-1.55 (m, 4H); 1.07 (t, J = 8, 3H)] and R_f in a variety of solvent systems. The nmr of the C-7 epimer 20 showed, as expected, phenolic protons at δ12.91 and δ12.01, as well as the characteristically broad C-7 pseudoaxial proton signal at δ5.37, $\nu_{\frac{1}{2}} \simeq$ 18 Hz.[8]

The above synthetic sequence (yield unoptimized), illustrated specifically for decarbomethoxyaklavinone, has been successfully adapted to the synthesis of both 11-deoxycarminomycinone and 11-deoxydaunomycinone by appropriate modification of the A-ring. Moreover, the introduction of the C-6 formyl group (as in the sequence 7 → 12) can be short cut in some instances. These extensions of our strategy will be reported in subsequent papers.

Acknowledgments: We are grateful to Professor Federico Arcamone (Farmitalia Carlo Erba) for providing us a comparison sample of decarbomethoxyaklavinone. Partial support of this work by grant CA 11326 from the National Cancer Institute and by a Pharmacology Training Grant Fellowship (T-32-GM-07141) to J.R. is gratefully acknowledged.

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8. All new compounds showed nmr, ir, ms and analysis as expected.

(Received in USA 30 November 1980)