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APPROACH TO THE AKLAVINONE SERIES THROUGH A NEW HIGH PRESSURE-INDUCED [BCD → ABCD] CYCLOADDITION STRATEGY

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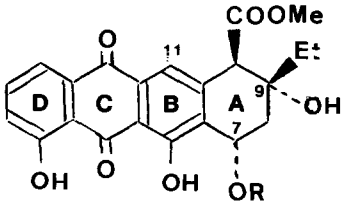
Summary : *The high pressure-induced cycloaddition of diene 3 with tricyclic enone 2 led to the tetracyclic adduct 4.*

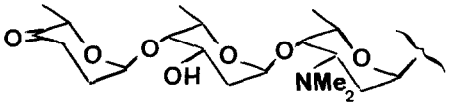
Aklavinone 1a is the aglycone component of several members of the family of antineoplastic antibiotics 11-deoxyanthracyclines [1], the most representative being aclacimomycin A 1b.

Owing to the absence of side-effects (myocardiotoxicity, alopecia), aclacinomycin A appears to be a major antitumor drug, especially for the treatment of acute myeloid leukemia as shown by a recent clinical investigation [2].



1a R = H

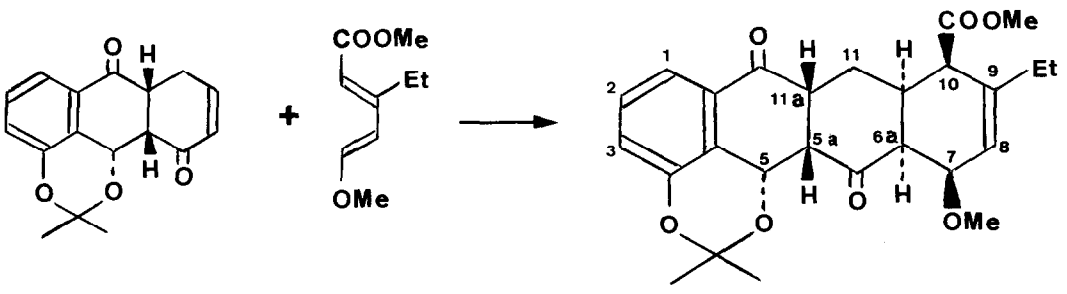
1b R =



Several syntheses of aklavinone have already been published [3]. In this paper we wish to report an efficient approach to this aglycone based on a new [BCD → ABCD] cycloaddition strategy that makes use of the tricyclic (cyclohexenone-like) dienophile 2 and diene 3 to secure the tetracyclic adduct 4.

The two main advantages of this route are : (i) construction of the A-ring with simultaneous introduction of all the functional groups (except the latent C-9 OH functionality) in their required oxidation states, (ii) the fact that, contrary to a related route published by T.T.Li [4], no activated quinone-like dienophile is needed for this crucial cycloaddition step (in Li's strategy an additional undesirable C-11 carbonyl group is thus introduced, which is subsequently somewhat difficult to remove).

Although according to our methodology the C-7 methoxy group is introduced with the "wrong" β configuration, this is irrelevant since epimerization of the OH group at this position in the final molecule is facile and gives the desired cis relationship between the C-7 and C-9 OH substituents [5].

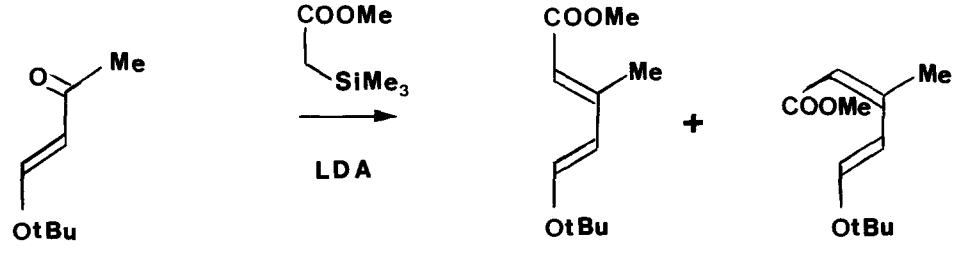


2 3 4

Diene synthesis

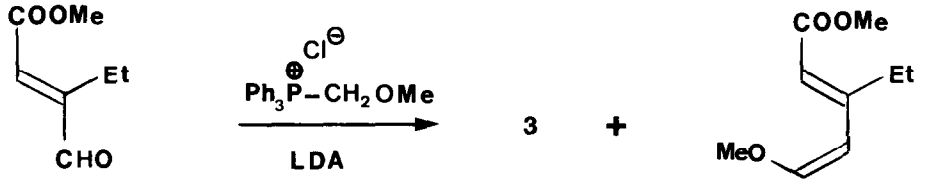
The required (E,E) [6] diene 3 bears an ester function and an alkoxy group at the ends of the diene moiety. This peculiar substitution, found in a new class of dienes we have previously synthesized [7], confers an interesting ambident reactivity in the Diels-Alder cycloaddition [7,8,9]. In the present case, the synthesis of compound 3 and related dienes is somewhat complicated by the presence of the additional alkyl substituent ; however we have developed two routes for these molecules.

Condensation of methyl lithiotrimethylsilylacetate [10] and enone 5 (1 equiv, THF, -78°C, 2 h, then "quenching" with H_2O at this temperature) led to a 2:1 (EE/ZE) mixture [6] of the expected dienes 6 [11] in 85 % combined yield.



5 6

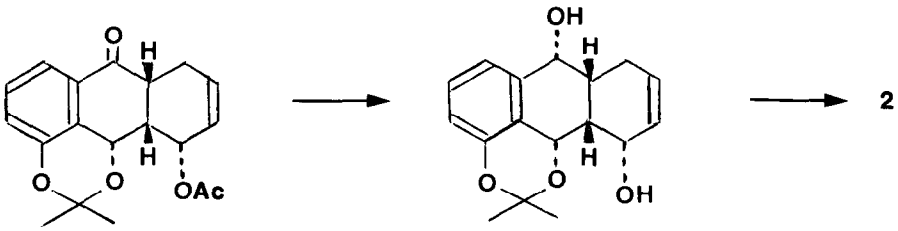
Although efficient, this methodology is limited by the difficult accessibility of the starting alkoxy-enones [12]; in contrast, the following procedure is more general. The reaction of methoxymethylene triphenylphosphorane with aldehyde 7 [13] (THF, -78°C, 30 min, then "quenching" with H_2O at this temperature) afforded a 2:1 (EE/EZ) mixture [6] of dienes [14] 3 and 8 in 70 % combined yield.



7 8

Dienophile unit synthesis

Racemic enone 2 [15] was obtained in 60 % overall yield starting from the known compound 9 [16] (LAH, THF, 0°C, then Swern oxidation of the intermediate diol 10 : oxalyl chloride 2.2 equiv, Et_3N/CH_2Cl_2, -40°C → 0°C).



9 10

Diels-Alder Reaction

This crucial step involves the cycloaddition of sensitive substrates enone 2 and diene 3. The sensitivity coupled with the notoriously poor (cyclohexenone-like) dienophilicity of 2 led us to focus our efforts on the high pressure activation technique [7,8,9,17] rather than conventional thermal or Lewis acid-catalyzed methods.

Activation by the combination of high pressure and slight heating was successful [9] (CH_2Cl_2/MeCN 3:1, 17 kbar, 65°C, 48 h) and gave regio and stereoselectively the expected tetracyclic adduct 4 [18] in 75 % yield.

The completion of the aklavinone synthesis starting from the now readily available tetracyclic adduct 4 is in progress.

REFERENCES and NOTES

1 "Daunomycin and related Antibiotics" in Topics in Antibiotic Chemistry, vol. 2, P.G. Sammes Editor, John Wiley & Sons, Chichester, 1978.

2 D. Machover, J. Gastiaburu, M. Delgado, E. Goldschmidt, R. Hulhoven, J.L. Misset, F. de Vassal, H. Tapiero, T. Dorval, P. Ribaud, L. Schwarzenberg, G. Mathé, Biomedicine & Pharmacotherapy, **38**, 328 (1984).

3 J.G. Bauman, R.C. Hawley, H. Rapoport, J. Org. Chem., **50**, 1569 (1985) and references cited therein. G.A. Kraus, J. Walling, Tetrahedron Lett., 1873 (1986).

4 T.T.Li, Y.L. Wu, T.C. Walsgrove, Tetrahedron, **40**, 4701 (1984).

5 B.A. Pearlman, J.M. McNamara, I. Hasan, S. Hatakeyama, H. Sekizaki, Y. Kishi, J. Am. Chem. Soc., **103**, 4248 (1981).

6 Since dienes of (E,E) geometry are the only reactive species in such cycloaddition processes, no separation of EE/EZ mixtures is required.

7 J. Maddaluno, J. d'Angelo, Tetrahedron Lett., 895 (1983).

8 G. Revial, M. Blanchard, J. d'Angelo, Tetrahedron Lett., 899 (1983).

9 C. Ferroud, G. Revial, J. d'Angelo, Tetrahedron Lett., 3981 (1985).

10 K. Shimoji, H. Taguchi, K. Oshima, H. Yamamoto, H. Nozaki, J. Am. Chem. Soc., **96**, 1620 (1974) ; S.L. Hartzell, D.F. Sullivan, M.W. Rathke, Tetrahedron Lett., 1403 (1974).

11 6 : ^{1}H NMR (90 MHz, $CDCl_3$) δ ppm : EE : 5.5 (s 1H) 5.65 (d J=12.7 Hz 1 H) 6.95 (d J=12.7 Hz 1 H) ; ZE : 5.3 (s 1 H) 6.95 (d J=12.7 Hz 1 H) 7.2 (d J=12.7 Hz 1 H).

12 Except enone 5 which was easily obtained from the corresponding commercially available methoxy derivative (tBuOH,p-toluenesulfonic acid, 85 %).

13 7 was obtained by condensation of butyraldehyde morpholinoenamine with methyl glyoxylate methyl half-acetal:S. Laugraud, A. Guingant, J. d'Angelo, to be published.

14 3+8 : ^{1}H NMR (90 MHz, $CDCl_3$) δ ppm : 3 : 5.4 (d J=12.7 Hz 1 H) 5.5 (s 1 H) 6.9 (d J= 12.7 Hz 1 H) ; 8 : 4.65 (d J=6.7 Hz 1 H) 6.0 (s 1 H) 6.05 (d J=6.7 Hz 1 H).

15 2 : white solid, no definite m.p. (dec.). ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm : 2.65 (dddd J=19 5.5 2.25 2.25 Hz 1 H) 3.21 (broad t J=5.0 Hz 1 H) 3.48 (dddd J=19.5 5.5 2.25 1.25 Hz 1 H) 3.53 (dd J=4.5 5 Hz 1 H) 5.30 (d J=4.5 Hz 1 H) 5.85 (ddd J=10 2.25 1.25 1 H) 6.85 (dddd J=10 5.5 2.25 0.9 Hz 1 H).

16 B.M. Trost, C.G. Caldwell, E. Murayama, D. Heissler, J. Org. Chem., **48**, 3252 (1983).

17 K. Matsumoto, A. Sera, Synthesis, 999 (1985).

18 4 : white solid, no definite m.p. (dec.) ^{1}H NMR (200 MHz, $CDCl_3$, double resonance assignments) δ ppm : 0.99 (t J=7.5 Hz 3 H) 1.57 (s 3 H) 1.70 (s 3 H) 2.44 (dd J=5.5 5.5 Hz 1 H_{6a}) 3.13 (m 1 H_{11a}) 3.24 (d J=5.5 Hz 1 H_{10}) 3.75 (s 3 H) 3.78 (dd J=5.5 5.5 Hz 1 H_7) 3.87 (s 3 H) 4.13 (dd J=5.75 4.5 Hz 1 H_{5a}) 5.11 (d J=4.5 Hz 1 H_5) 5.89 (m 1 H_8) 7.02 (dd J=8.0 1.2 1 H_3) 7.23 (dd J=7.5 8.0 Hz 1 H_2) 7.46 (dd J=7.5 1.2 Hz 1 H_1).

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