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A REGIOSPECIFIC TOTAL SYNTHESIS OF (±)-DAUNOMYCINONE

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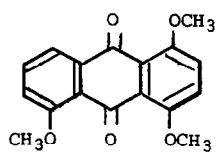
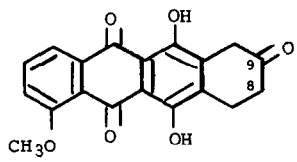
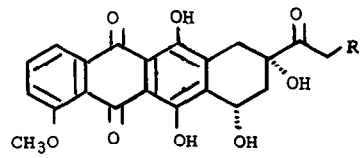
The pioneering work of Wong et al in 1971-73[1] was the first of a growing series of investigations toward the efficient laboratory synthesis of clinically useful anthracycline antibiotics. Although several total syntheses of (±)-daunomycinone (IIIa) and adriamycinone (IIIb) have been reported,[2] only recently have regiospecific syntheses of these molecules been achieved.[3] In 1976 we described the conversion of our red tetracyclic ketone II to (±)-daunomycinone in approximately 10% yield.[4] However, our three step preparation of ketone II from 1,4,5-trimethoxyanthraquinone (I) by a Diels-Alder route was nonregiospecific, generating an equal amount of the corresponding C-8 ketone which had to be tediously separated from II. We now report a strategy which leads uniquely to isomer II, thereby comprising a regiospecific total synthesis of (±)-daunomycinone and its congeners.



I



II

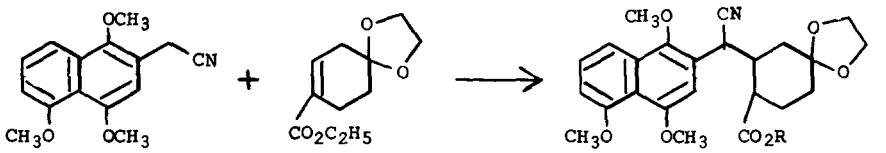


IIIa R = H

b R = OH

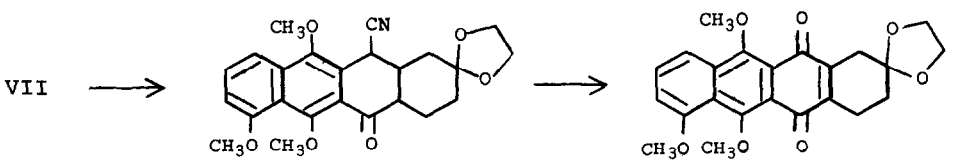
Our control strategy involves the conjugate addition of 1,4,5-trimethoxynaphthylacetonitrile (IV)[5] to the readily available cyclohexene ester ketal V, an approach independently developed by Parker and Kallmerten on different substrates.[6] Optimum conditions for our Michael addition were to add a THF solution of ester V to the enolate of nitrile IV (from NaH in THF) at 0°. After

8 hrs at 0° the reaction was allowed to warm to r.t. overnight. Workup followed by Si gel filtration (ether) gave 94% of a solid, mp 165-170°, corresponding to the diastereomeric mixture of adducts VI.[7]



IV V VI R = C_2H_5
VII R = H

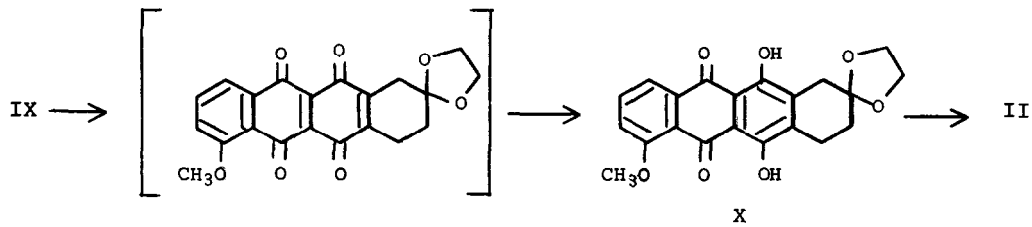
Hydrolysis of VI in 95% ethanolic KOH (1 N, r.t., 2 days) gave 85% of cyanoacids VII as a colorless solid, mp 253-257°. Cyclization of VII in 2:1 CF_3CO_2H—$(CF_3CO)_2O$ at r.t. for 12 hrs, followed by reketalization at C-9 ($HOCH_2CH_2OH$, p-TSa, C_6H_6, reflux, 2 hrs)[8] gave in 89% yield the tetracyclic cyanoketal VIII as a diastereomeric mixture, mp 267-270°. Enolate oxidation of VIII by the procedure of Watt[9] (2 eqts LDA, 5:1 THF-HMPA, -78°, O_2, then 0°, followed by aq. Na_2SO_3) led in 70% yield after Si gel chromatography (1:1 EtOAc-hexane) to an orange solid identified by mass spectrum (m/e = 410, M^+, base peak) and nmr [δ1.88 (t, J = 6 Hz, 2H); 2.81 (s, 2H); 2.87 (t, J = 7 Hz, 2H); 3.95, 4.00, 4.02 (3s, 13 H); 7.07 (d, J = 8 Hz, 1H); 7.60 (t, J = 8 Hz, 1H); 7.97 (d, J = 8 Hz, 1H)] as the quinone IX.[10]



VII VIII IX

Attempts to carry out reductive acetylation of IX (as in our recent isobenzofuran route)[2b] followed by C-ring oxidation were unsuccessful in this

series. Therefore quinone IX was oxidatively demethylated[11] by AgO (acetone, 6 N HNO_3, 5 mins. r.t.) followed by bisulfite workup to give the anthraquinone ketal X [nmr: δ1.98 (t, J = 7 Hz, 2H); 2.99 (s, 2H); 3.06 (t, J = 7 Hz, 2H); 4.07 (s, 7H); 7.35 (d, J = 8 Hz, 1H); 7.74 (t, J = 8 Hz, 1H); 8.02 (d, J = 8 Hz 1H); 13.45 (s, 1H); 13.84 (s, 1H)]. Mild deketalization (1:1 CF_3CO_2H—10% HCl, r.t., 6 hrs) gave the red ketone II, mp 252-255°, in 70% yield from IX. The high resolution nmr and chromatographic properties of this material were identical to those of authentic isomer II prepared by our earlier procedure.



X

Since nitrile IV is available in 36% yield from 1,5-dihydroxynaphthalene and can be transformed as shown into ketone II in 35% yield over six steps, the latter compound becomes available by a convergent route in about 13% yield from a commercial precursor. Thus our synthesis leads to (±)-daunomycinone in yield and number of steps comparable to other regiospecific routes recently completed.

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References and Notes

1. C. M. Wong, D. Popien, R. Schwenk and J. TeRaa, Can. J. Chem., 49, 2712 (1971); C. M. Wong, R. Schwenk, D. Popien and T. L. Ho, ibid., 51, 466 (1973).
2. (a) R. D. Gleim, S. Trenbeath, R. S. D. Mittal and C. J. Sih, Tetrahedron Lett., 3385 (1976); (b) A. S. Kende, D. P. Curran, Y. Tsay and J. Mills, ibid., 3537 (1977). See also References 1, 3 and 4.
3. P. W. Raynolds, M. J. Manning and J. S. Swenton, Tetrahedron Lett., 2383 (1971); J. S. Swenton and P. W. Raynolds, J. Am. Chem. Soc., 100, 6188 (1978); F. Suzuki, S. Trenbeath, R. D. Gleim and C. J. Sih, ibid., 100, 2272 (1978). For an elegant regiospecific approach see T. R. Kelly, J. W. Gilliard, R. N. Goerner and J. M. Lyding, ibid., 99, 5513 (1977).
4. A. S. Kende, Y. Tsay and J. E. Mills, J. Am. Chem. Soc., 98, 1967 (1976).
5. Nitrile IV, mp 110-111°, was prepared in 63% overall yield from 2-allyl-5 methoxynaphthoquinone [W. Eisenhuth and H. Schmid, Helv. Chim. Acta, 41, 2021 (1958)] by sodium dithionite in ether [T.-T.Li and R.H.Ellison, J.Am. Chem. Soc., 100, 6263 (1978)], methylation with NaH and MeI in DMF-THF, double bond cleavage with cat. OsO_4—$NaIO_4$ [R. Pappo et al., J. Org. Chem., 21, 478 (1956)] and reaction of the resulting aldehyde with H_2NOSO_3H in aqueous methanol [J. Streith and C. Fizet, Helv. Chim. Acta, 59, 2786 (1976)].
6. K. A. Parker and J. L. Kallmerten, Tetrahedron Lett., 4557 (1977).
7. All mp were taken on a Mel-Temp melting point apparatus and are uncorrected. All compounds gave mass spectrometric or combustion analyses as well as nmr and ir spectra in agreement with the proposed structure.
8. The conjugated ketone is untouched under these conditions.
9. S. J. Selikson and D. S. Watt, J. Org. Chem., 40, 267 (1975).
10. An analogous oxidation product has been isolated by the Brown University group in a related series (K. A. Parker and J. L. Kallmerten, personal communication).
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