

Total Synthesis of 11-Deoxydaunomycinone¹

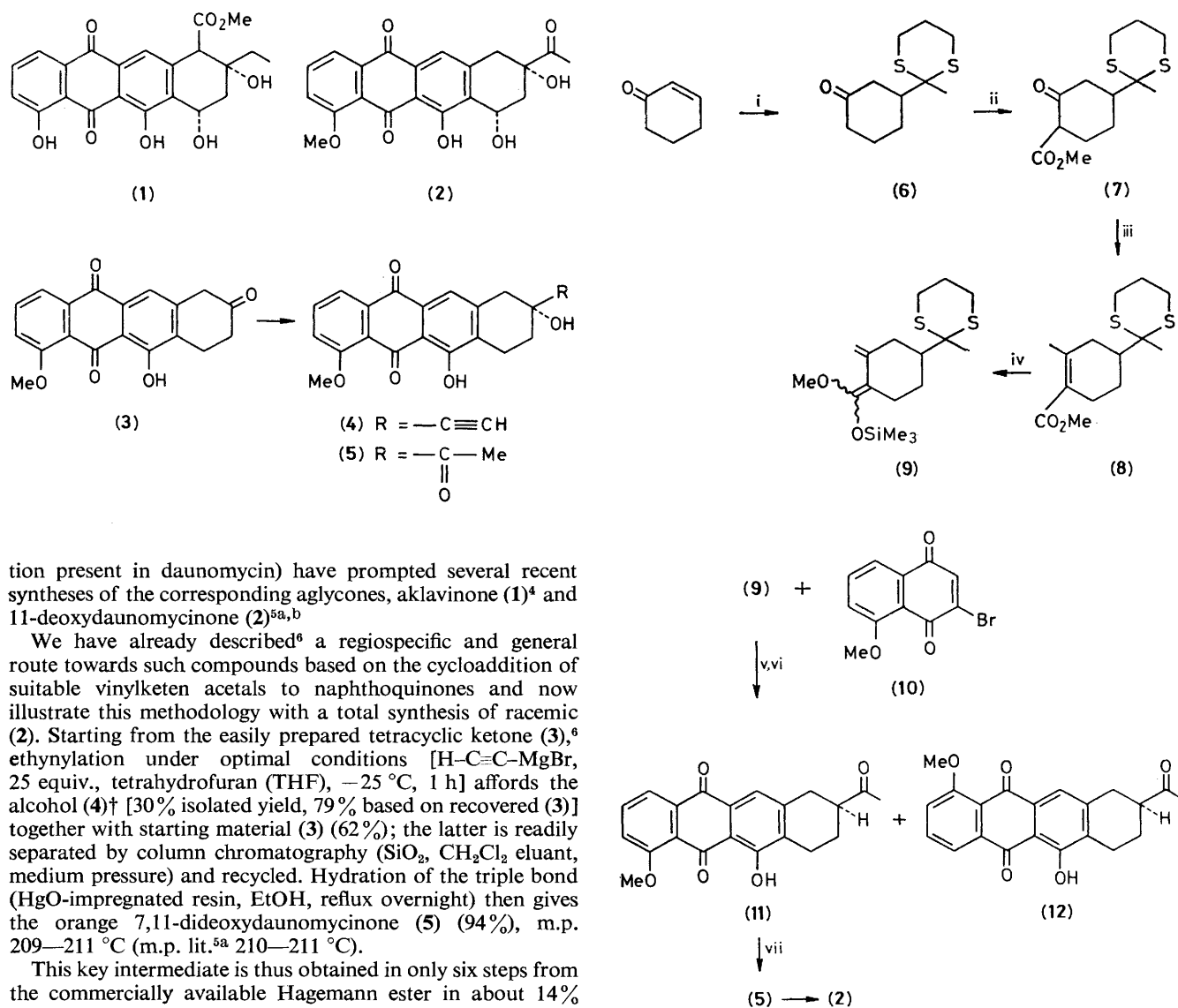
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11-Deoxydaunomycinone (**2**), the aglycone of a recently isolated antitumour anthracycline, is prepared using two different routes in only seven and eight steps respectively.

The search for new anthracyclines with better therapeutic indices is of great interest and the synthesis of modified aglycones, directly involved in the intercalation process with DNA, appears to be of crucial importance to studies of

structure-activity relationships. The known high antitumour activity and lower toxicity (compared to daunorubicin itself) of aclacinomycin A² and the recent isolation of 11-deoxydaunomycin³ (both compounds lack the C-11-hydroxy-func-



tion present in daunomycin) have prompted several recent syntheses of the corresponding aglycones, aklavinone (1)⁴ and 11-deoxydaunomycinone (2)^{5a,b}

We have already described⁶ a regiospecific and general route towards such compounds based on the cycloaddition of suitable vinylketen acetals to naphthoquinones and now illustrate this methodology with a total synthesis of racemic (2). Starting from the easily prepared tetracyclic ketone (3),⁶ ethynylation under optimal conditions [$\text{H}-\text{C}\equiv\text{C}-\text{MgBr}$, 25 equiv., tetrahydrofuran (THF), -25°C , 1 h] affords the alcohol (4)[†] [30% isolated yield, 79% based on recovered (3)] together with starting material (3) (62%); the latter is readily separated by column chromatography (SiO_2 , CH_2Cl_2 eluant, medium pressure) and recycled. Hydration of the triple bond (HgO -impregnated resin, EtOH, reflux overnight) then gives the orange 7,11-dideoxydaunomycinone (5) (94%), m.p. 209–211 $^\circ\text{C}$ (m.p. lit.^{5a} 210–211 $^\circ\text{C}$).

This key intermediate is thus obtained in only six steps from the commercially available Hagemann ester in about 14% overall yield without recycling of (3).

However the incomplete conversion of (3) to (4) prompted us to develop an alternative approach to (5) (Scheme 1). The required vinylketen acetal (9) was prepared in five steps: 1,4-addition of 2-lithio-2-methyl-1,3-dithian to cyclohexenone gives (6)⁷ quantitatively which is then regiospecifically methoxycarbonylated to (7) and subsequently converted to (8), following the procedure of Weiler⁸ in a single pot reaction. Kinetic deprotonation with lithium di-isopropylamide (LDA) of (8) followed by trimethylsilyl chloride (TMSCl) quenching of the intermediate dienolate and non-aqueous work-up affords the sensitive keten acetal (9) as a pale yellow oil in about 40% overall yield from cyclohex-2-en-1-one.

Cycloaddition of (9) (1.1 equiv.) to 3-bromo-5-methoxy-1,4-naphthoquinone (10)⁹ gives after acidic work-up and oxidative cleavage of the protective dithian group the known ketone (11), m.p. 221–223 $^\circ\text{C}$ (m.p. lit.^{5b} 223–226 $^\circ\text{C}$) in 71% overall yield from (10). Under these conditions trace amounts (1.3%) of the regio-isomeric ketone (12) are isolated. Hydroxylation at C-9 to give (5) is carried out using the procedure of Gardner¹⁰ [Bu^tOK , O_2 , $(\text{EtO})_3\text{P}$, dimethylformamide (DMF), -30°C ,

Scheme 1. Reagents and conditions: i, $\text{Me}(\text{Li})\text{CS}[\text{CH}_2]_3\text{S}$, THF-hexamethylphosphoramide, -78°C ; ii, $\text{CO}(\text{OMe})_2$, NaH, benzene, cat. MeOH, reflux; iii, NaH, THF, 0°C , $(\text{EtO})_3\text{POCl}$ 1.1 equiv., 20°C , 1 h; then Me_2CuLi 1.5 equiv., ether, -78°C to $+20^\circ\text{C}$; iv, LDA, SiMe_3Cl ; v, THF, 0 to 20°C , 16 h; vi, HgCl_2 2 equiv., CaCO_3 2 equiv., $\text{MeCN}-\text{H}_2\text{O}$, 5 h reflux; vii, Bu^tOK , O_2 , $(\text{EtO})_3\text{P}$, DMF, -30°C , 5 h.

5 h] in yields ranging from 21 to 40% together with recovered (5).[‡]

The final step (hydroxylation at C-7) is done as in the daunomycin series by benzylic bromination followed by displacement of the labile benzylic bromine atom. However only extensive aromatization is observed under standard conditions (excess of Br_2 , hv, CCl_4 , 20°C ,^{11a} or *N*-bromosuccinimide, CCl_4 , reflux^{11b}) and we have therefore found that this functionalization is best carried out using 1.1 equiv. of Br_2 in CCl_4 (irradiation, 100 W lamp) in presence of 4–5 equiv. of cyclohexene oxide as HBr scavenger.¹² Displacement with excess of $\text{Ca}(\text{OH})_2$ in wet THF then gives a mixture of (2) (9%) and the corresponding 7 β -isomer (54%).

[†] Satisfactory analytical and spectroscopic data have been obtained for all new compounds.

[‡] Numerous efforts to get higher reproducible yields were unsuccessful.

Epimerization of the unwanted isomer is difficult to achieve owing to the exceptionally easy aromatization observed in this series§ but affords a 3 : 1 ratio in favour of (2) in CF₃CO₂H at 0 °C.

Our synthetic (±)-(2) is identical in all respects (m.p., t.l.c., spectroscopic data) to natural 11-deoxydaunomycinone kindly provided by Dr G. Cassinelli (Farmitalia-Carlo Erba).

We thank Prof. J. C. Jacquesy for helpful discussions and the C.N.R.S. for financial support.

Received, 25th January 1982; Com. 072

References

- 1 Presented in part at ESOC II, June 1981, Stresa, Italy.
- 2 T. Oki, 'Anthracyclines: Current Status and New Developments,' eds. S. T. Crooke and S. D. Reich, Academic Press, 1980, ch. 19, p. 323.
- 3 F. Arcamone, G. Cassinelli, F. Di Matteo, S. Forenza, M. C. Ripamonti, G. Rivola, A. Vigevani, J. Clardy, and T. McCabe, *J. Am. Chem. Soc.*, 1980, **102**, 1462.
- 4 A. S. Kende and J. P. Rizzi, *J. Am. Chem. Soc.*, 1981, **103**, 4247; B. A. Pearlman, J. M. McNamara, I. Hasan, S. Matakeyama, M. Sekizaki, and Y. Kishi, *ibid.*, p. 4248. P. N. Confalone and G. Pizzolato, *ibid.*, p. 4251; Tsung-Tee Li and Yu Lin Wu, *ibid.*, p. 7007.
- 5 (a) S. D. Kimball, D. R. Walt, and F. Johnson, *J. Am. Chem. Soc.*, 1981, **103**, 1561; (b) for a synthesis of (5) see J. Yadav, P. Corey, Chi-Tung Hsu, K. Perlman, and C. J. Sih, *Tetrahedron Lett.*, 1981, 811; (c) for a synthesis of 11-deoxy-carminomycinone see A. S. Kende and S. D. Boettger, *J. Org. Chem.*, 1981, **46**, 2799; (d) for a synthesis of 4-demethoxy-11-deoxydaunomycin and adriamycin see H. Umezawa, Y. Takahashi, M. Kinoshita, and H. Naganawa, *J. Antibiot.*, 1980, **33**, 1581.
- 6 J. P. Gesson, J. C. Jacquesy, and M. Mondon, *Tetrahedron Lett.*, 1980, 3351. The overall yield of (3) from Hagemann ester has been improved to about 50%. For alternative routes see: J. G. Bauman, R. B. Barber, R. D. Gless, and H. Rapoport, *Tetrahedron Lett.*, 1980, 4777; J. Alexander, D. L. Flynn, L. A. Mitscher, and T. Veysoglu, *Tetrahedron Lett.*, 1981, 3711.
- 7 C. A. Brown and A. Yamaichi, *J. Chem. Soc., Chem. Commun.*, 1979, 100.
- 8 F. W. Sum and L. Weiler, *Can. J. Chem.*, 1979, **57**, 1431.
- 9 R. H. Thomson, *J. Org. Chem.*, 1948, **13**, 377; R. L. Hannan, R. B. Barber, and H. Rapoport, *ibid.*, 1979, **44**, 2153.
- 10 J. N. Gardner, F. E. Carlon, and O. Gnoj, *J. Org. Chem.*, 1968, **33**, 3294.
- 11 (a) A. S. Kende, Y. Tsay, and J. E. Mills, *J. Am. Chem. Soc.*, 1976, **98**, 1969; (b) T. H. Smith, A. N. Fujiwara, W. W. Lee, H. Y. Wu, and D. W. Henry, *J. Org. Chem.*, 1977, **42**, 3653.
- 12 V. Carlo, L. Lopez, and G. Pesce, *J. Chem. Soc., Perkin Trans. 1*, 1977, 501.

§ Hydroxylation proceeds in better yield starting from the corresponding 4-demethoxy compound, owing to a slower aromatization (J. P. Gesson, J. C. Jacquesy, and M. Mondon, unpublished results, see also ref. 5d).