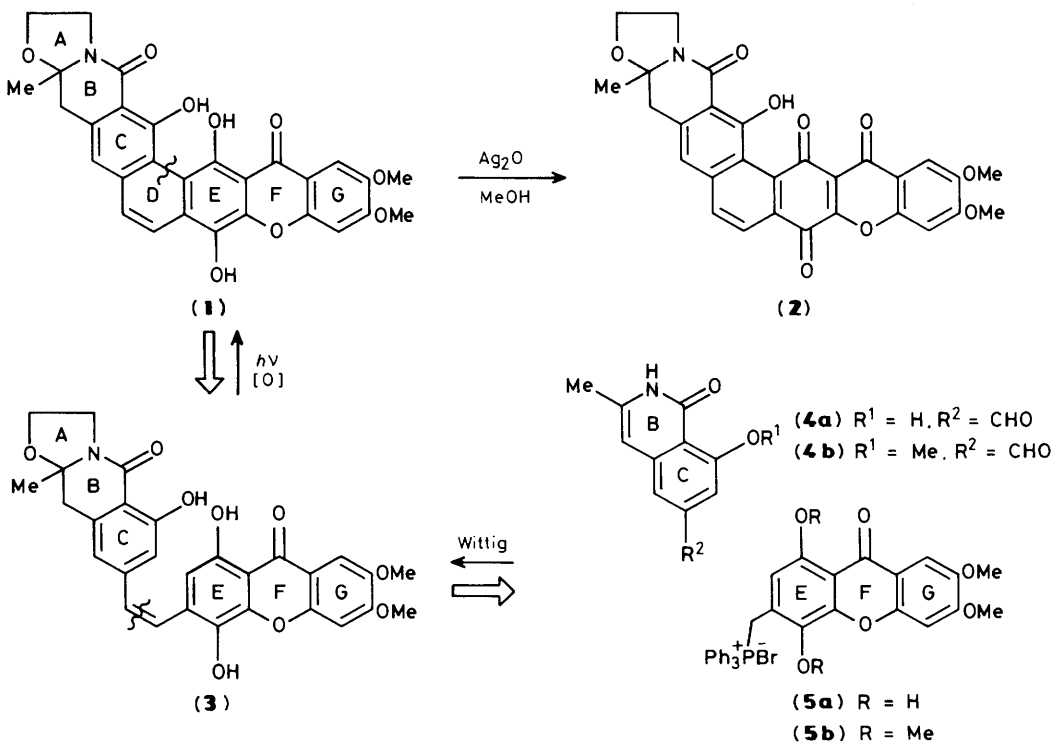
Synthetic Studies towards Novel Xanthone Antibiotics, Cervinomycins

Goverdhan Mehta* and Yenamandra Venkateswarlu

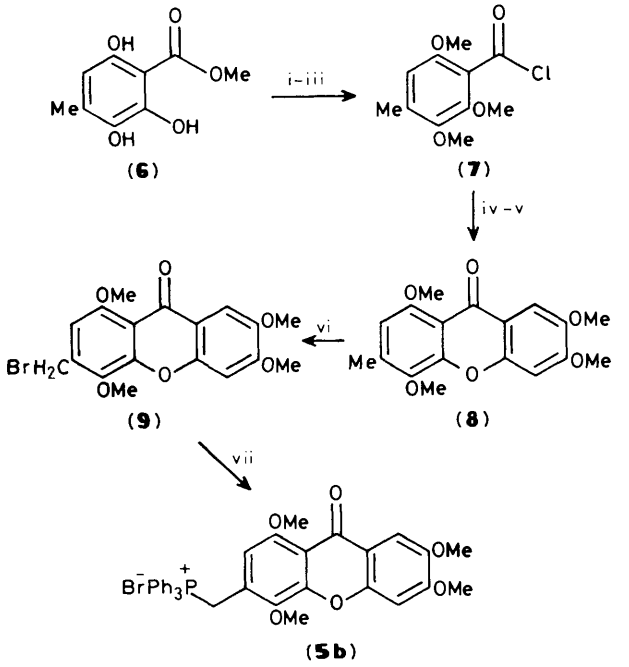
School of Chemistry, University of Hyderabad, Hyderabad 500 134, India

The xanthone (EFG) and isoquinolone (BC) segments of cervinomycins have been synthesised, xanthone (**5b**) has been naphthoannulated to the pentacyclic CDEFG portion of the antibiotic.

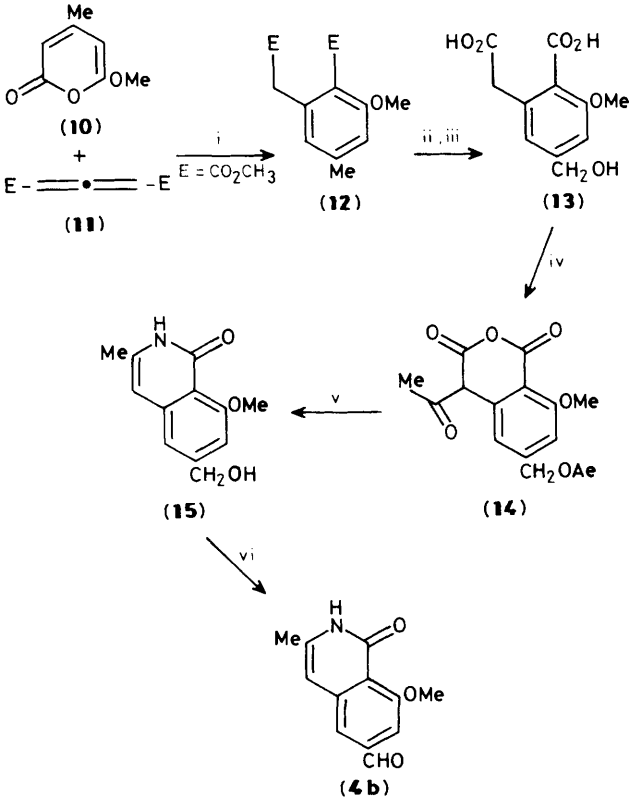
In 1986, Ōmura *et al.*[1a] elucidated the structures of novel xanthone antibiotics cervinomycin-A_1 (**1**) and A_2 (**2**), isolated earlier[1b] by them from *Streptomyces cervinus* sp.nov. Both (**1**) and (**2**) have been shown to be highly active against anaerobic bacteria and to a lesser extent against mycoplasma and some Gram-positive bacteria.[1a—c] Structurally, cervinomycins belong to a small but biologically potent family of antibiotics consisting of lysolipin I,[2a] albofungin (Kanchanomycin), Chloroalbofungin,[2b] and LL-D42067 α & β,[2c] all of which possess a basic hexacyclic structure with xanthone and isoquinolone moieties being most conspicuous. Surprisingly, no synthetic studies directed towards these antibiotics have been reported. We considered various approaches to cervinomycins but viewed the retrosynthetic protocol indicated in Scheme 1 with particular attention as it identified the xanthone [EFG fragment (**5a**)] and isoquinolone [BC fragment (**4a**)] as the key building blocks, which could be readily joined together with the photocyclisation (**3** → **1**) being the pivotal



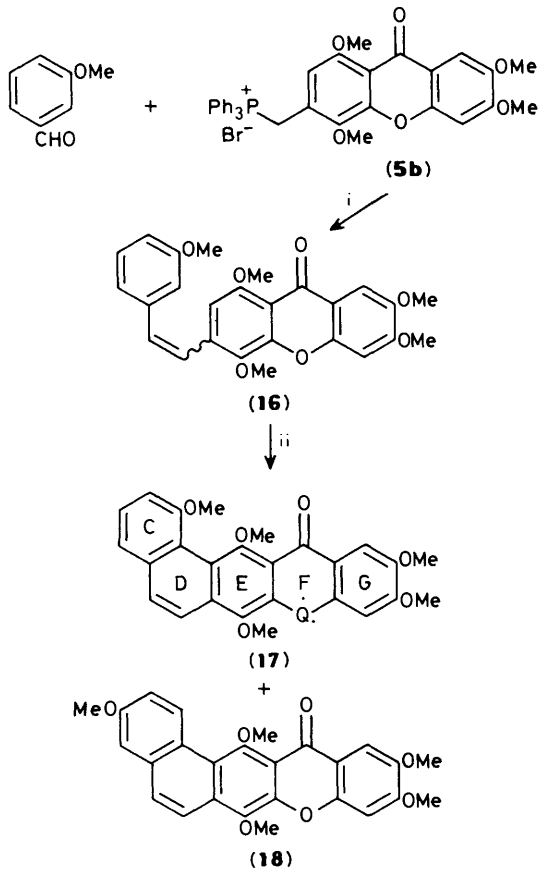
Scheme 1



Scheme 2. *Reagents and conditions:* (i) MeI–K_2CO_3–acetone, heat, 12 h, 87%. (ii) 4 M NaOH, EtOH, room temp., 12 h, 92%. (iii) $SOCl_2$, heat, 4 h, 95%. (iv) 1,2,4-trimethoxybenzene, $AlCl_3$, ether, room temp., 18 h. (v) K_2CO_3–aq.MeOH, heat, 16 h, 37% from (**7**). (vi) *N*-bromosuccinimide, (azoisobutyronitrile AIBN), CCl_4, heat, 16 h, 60%. (vii) Ph_3P, toluene, heat 3 h, quant.



Scheme 3. *Reagents and conditions:* (i) *o*-dichlorobenzene-sealed tube, 150—165 °C, 3 days, 55%. (ii) NBS–AIBN, CCl_4, heat, 2 h, 60%. (iii) aq.KOH–MeOH, heat, 3 h, 96%. (iv) Ac_2O–Py, room temp., 3 h, 70%. (v) aq.NH_3, heat, 3 h, 30%. (vi) Jones' reagent, Me_2CO, 0—5 °C, 37%.



Scheme 4. *Reagents and conditions:* (i) K_2CO_3, 18-crown-6, THF, heat, 18 h, 90%. (ii) *hν* (450 W, Pyrex), benzene–I_2, 3 h, 10% [of (**17**) + (**18**)].

step. We now report the synthesis of xanthone (**5b**) and isoquinolone (**4b**) and describe model studies on the photonaphthoannulation of (**5b**).

While many natural and synthetic xanthones are known,[3] none having the substitution pattern of (**5a,b**) have been reported previously. Therefore, a synthesis of (**5b**) was developed from readily available 2,3,6-trihydroxy-*p*-toluic acid methyl ester (**6**)[4] as summarised in Scheme 2. Acylation of 1,2,4-trimethoxybenzene with the acid chloride (**7**) furnished the intermediate hydroxybenzophenones which were directly cyclised[5] with dilute base to furnish 1,4,6,7-tetramethoxy-5-methylxanthone (**8**)† quite uneventfully. Benzylic

† All compounds reported here were characterised on the basis of spectroscopic and microanalytical/m.s. data.

Compound (**8**): m.p. 156—157 °C, u.v. (MeOH): λ_{max} 361, 228, 268, 249 nm; i.r. (KBr): 1660, 1640, 1620, 1500, 840, 800 cm^{-1}; ^1H n.m.r. ($CDCl_3$, 100 MHz): δ 7.6 (1H, s), 6.92 (1H, s), 6.52 (1H, s), 4.0 (3H, s), 3.96 (3H, s), 3.93 (3H, s), 3.92 (3H, s), 2.4 (3H, s). (**9**): m.p. 100—201 °C, i.r. (KBr): 1680, 1640, 1620, 1500, 1300; ^1H n.m.r. ($CDCl_3$, 100 MHz): δ 7.6 (1H, s) 6.82 (1H, s), 6.72 (1H, s), 4.6 (2H, s), 4.08 (3H, s), 4.01 (3H, s), 3.98 (3H, s), 3.96 (3H, s). (**4b**): m.p. 179—180 °C (decomp.), i.r. (KBr): 3400, 1700, 1680, 1560, 1380, 1180, 1120 cm^{-1}; ^1H n.m.r. ($CDCl_3$, 100 MHz): δ 10.05 (1H, s), 7.48 (1H, s), 7.23 (1H, s), 6.32 (1H, s), 4.2 (3H, s), 2.4 (3H, s). (**17**): m.p. 125—126 °C, i.r. (KBr): 1620, 1460, 1260 cm^{-1}; ^1H n.m.r. ($CDCl_3$, 100 MHz): δ 7.89 (1H, d, *J* 8 Hz), 7.66 (1H, s), 7.60 (1H, d, *J* 8 Hz), 7.50—7.0 (3H, m), 6.93 (1H, s), 4.08 (3H, s), 4.0 (3H, s), 3.98 (3H, s), 3.95 (3H, s), 3.51 (3H, s). (**18**): m.p. 261 °C, i.r. (KBr): 1620, 1520, 1280 cm^{-1}; ^1H n.m.r. ($CDCl_3$, 100 MHz): δ 9.68 (1H, d, *J* 8.5 Hz), 8.15 (1H, d, *J* 8 Hz), 7.8 (1H, d, *J* 8 Hz), 7.76 (1H, s), 7.39—7.26 (2H, m), 7.03 (1H, s), 4.19 (3H, s), 4.07 (3H, s), 4.04 (3H, s), 4.02 (3H, s), 4.0 (3H, s).

bromination of (**8**) proceded smoothly with *N*-bromosuccinimide (NBS) and the resulting bromide (**9**)† was transformed to the required triphenylphosphonium bromide (**5b**), Scheme 2.

The fully functionalised isoquinolone (**4b**), representing the BC ring fragment of cervinomycins was synthesised in a sequence depicted in Scheme 3. Dimethyl homophthalate (**12**), available[6] through regioselective Diels–Alder reaction between α-pyrone (**10**) and allene diester (**11**) was converted into the hydroxymethyl compound (**13**) in two steps. Pyridine-catalysed acylation of (**13**) furnished the 4-acetylisochroman-1,3-dione derivative (**14**)† in one step.[7] The isochromandione (**14**) on treatment with aqueous ammonia yielded the hydroxymethylisoquinolone (**15**), which on controlled oxidation led to the desired (**4b**).[6]

With the BC and EFG fragments of (**1**) and (**2**) available, a model study was first executed for the naphthoannulation of xanthone and the construction of ring D. Wittig reaction between (**5b**) and *m*-methoxybenzaldehyde furnished the stilbene derivative (**16**) in which the *trans*-isomer predominated. Irradiation of a benzene solution of (**16**) in the presence of iodine furnished a mixture of two pentacyclic compounds (**17**) and (**18**) (4:1) in low yield. Both (**17**) and (**18**) where characterised on the basis of their spectroscopic data† and the major product was shown to correspond to the CDEFG portion of cervinomycin A_1 (**1**), Scheme 4. However, the presence of the xanthone moiety (triplet sensitizer) in (**16**) perhaps inhibits the direct photocyclisation and accounts for the low yield in the (**16**) → (**17**) + (**18**) reaction. Further extension of the present study towards the natural products (**1**) and (**2**) employing (**4b**) and modified (**5b**) is currently being pursued.

This research was supported by U.G.C. through a Special Assistance Programme and COSIST Support in Organic Synthesis.

Received, 22nd April 1988; Com. 8/01591K

References

1 (a) S. Ōmura, A. Nakagawa, K. Kushida, and G. Lukacs, *J. Am. Chem. Soc.*, 1986, **108**, 6088; (b) S. Ōmura, Y. Iwai, K. Hinotozawa, Y. Takanashi, J. Kato, and A. Nakagawa, *J. Antibiot.*, 1982, **35**, 645; (c) A. Nakagawa, S. Ōmura, K. Kushida, H. Shimizu, and G. Lukacs, *ibid.*, 1987, **40**, 301.
2 (a) M. Dobler and W. Keller-Schierlein, *Helv. Chim. Acta*, 1977, **60**, 178; (b) A. I. Gurevich, M. G. Karapetyan, M. N. Kolosov, V. N. Omelchenko, V. V. Onoprienko, G. I. Petrenko, and S. A. Popravko, *Tetrahedron Lett.*, 1972, 1751; (c) Quoted in ref. 1c.
3 M. U. S. Sultanbawa, *Tetrahedron*, 1980, **36**, 1465; J. E. Roberts, *Chem. Rev.*, 1961, **61**, 591.
4 D. H. R. Barton, L. Bould, D. L. J. Clive, P. D. Magnus, and T. Hase, *J. Chem. Soc.* (*C*), 1971, 2204.
5 A. J. Quillinan and F. Scheinmann, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1329.
6 Y. Tamura, F. Kukata, T. Rsugoshi, M. Sasho, Y. Nakajima, and Y. Kita, *Chem. Pharm. Bull.*, 1984, **32**, 3259.
7 R. B. Tirodkar and R. N. Usgaonkar, *Indian J. Chem.*, 1972, **10**, 679; A. R. Modie and R. N. Usgaonkar, *ibid.*, 1979, **17b**, 360.