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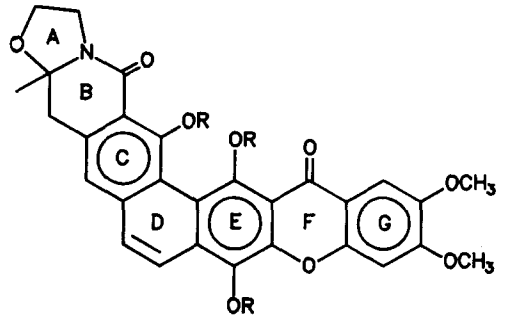
Total Synthesis of Cervinomycin A_1-trimethyl Ether and Cervinomycin A_2-methyl Ether

Goverdhan Mehta* **and Shailesh R. Shah**
School of Chemistry, University of Hyderabad, Hyderabad - 500 134, India.

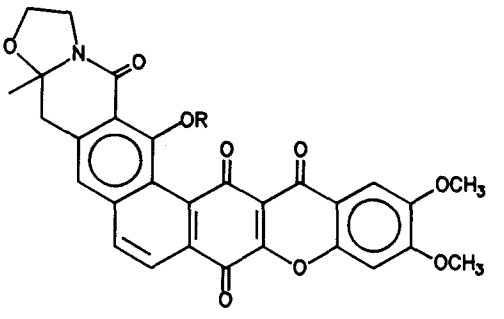
Key Words: Xanthone antibiotics; photocyclisation; tetrahydrooxazolo-[3,2-b]benz(g)isoquinolone formation.

Abstract: The heptacyclic framework of cervinomycin antibiotics has been constructed through a C+EFG → CEFG → CDEFG → ABCDEFG approach in which the photochemical generation of ring D was a key step.

The cervinomycins A_1 1 and A_2 2a belong to a small but structurally novel and biologically potent family of antibiotics that are recognisable through the conspicuous presence of xanthone and isoquinolone moieties within their polycyclic framework.[1] Ever since their isolation[2a] from Streptomyces cervinus sp. nov. and structure determination in 1986,[2b,c] cervinomycins have attracted the attention of synthetic chemists, particularly in view of their promising activity against anaerobic bacteria, mycoplasma and some Gram-positive bacteria.[2a] A synthesis of cervinomycins A_1 and A_2 has been recently reported[3a] in quick succession to the model studies in the area.[3b-d] Herein, we report the synthesis of cervinomycin A_1-trimethyl ether 3 and cervinomycin A_2-monomethyl ether as the culmination of our approach,[3b] in which the key central ring D is constructed through a photochemical electrocyclisation stratagem.



1· R = H
3· R = CH_3

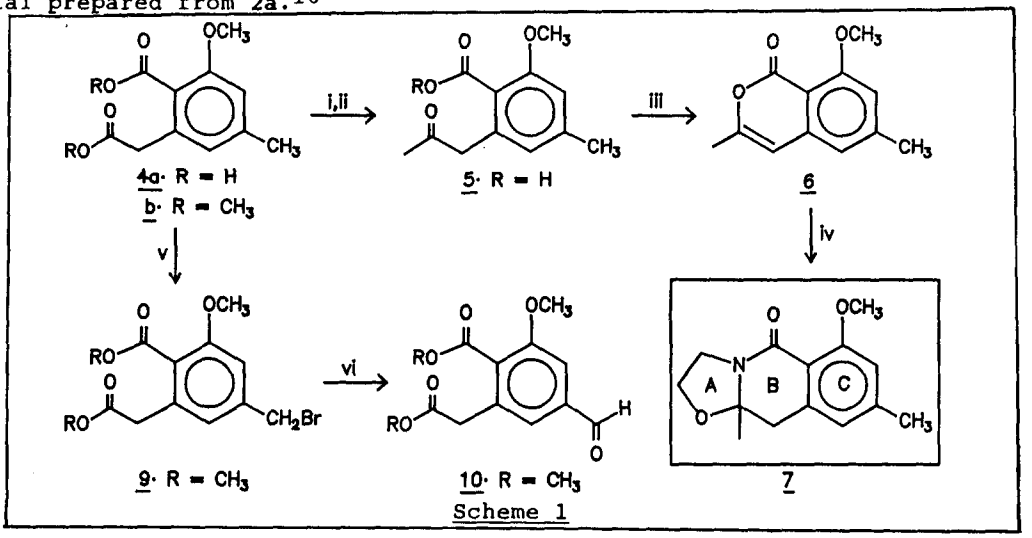


2a· R = H
b· R = CH_3

For the amplification of our earlier studies towards the synthesis of 1 and 2a, the main task was the construction of the sensitive tetrahydrooxazolo[3,2-b]benz(g)isoquinolone segment representing ABC rings of the natural products. After considerable efforts, a reliable sequence leading to the tricyclic portion 7[4] was developed from the homophthalic acid derivative 4[5] via the keto-acid 5 and isocoumarin 6[4,6], Scheme 1. Attempts

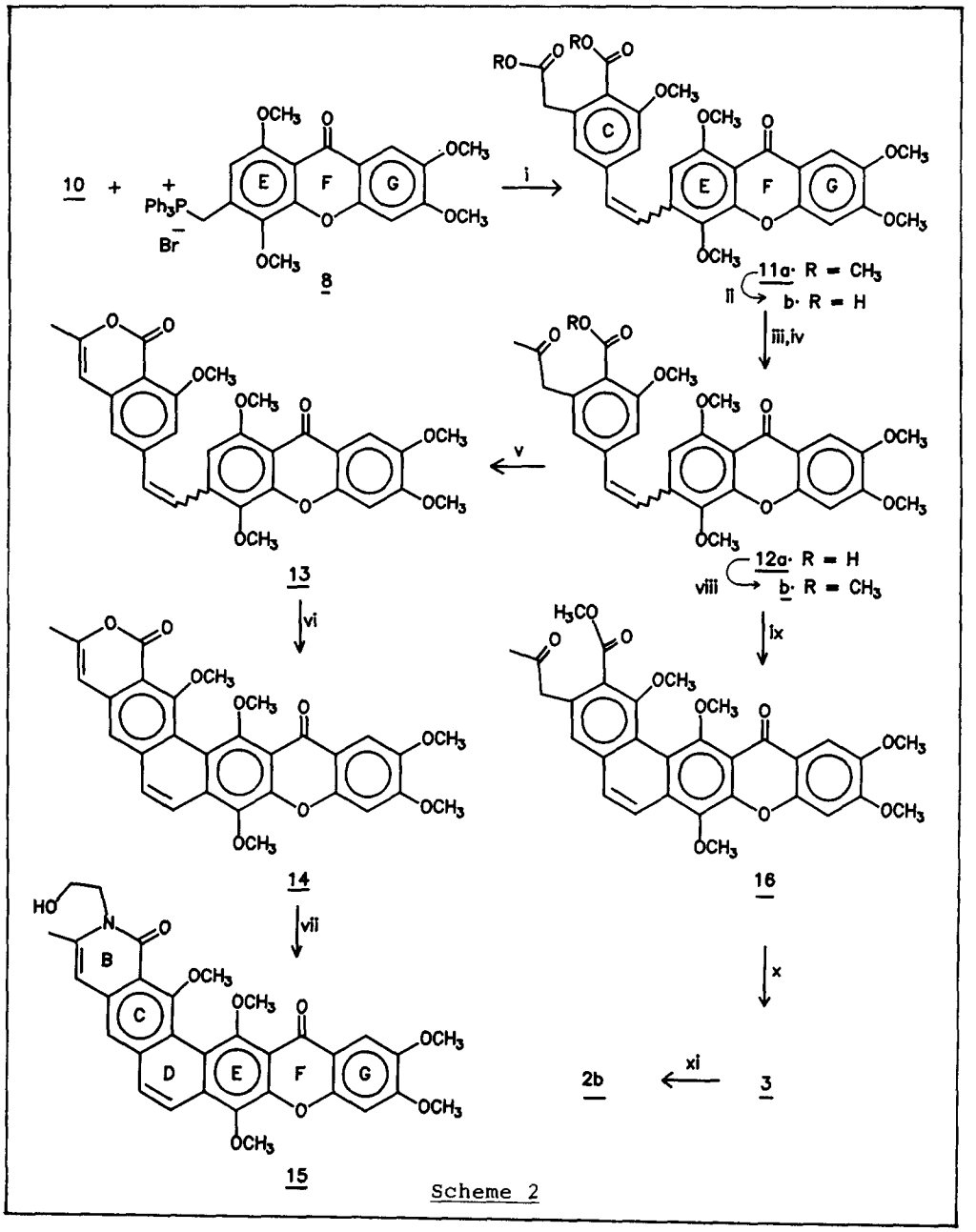
were then made to functionalise the aromatic methyl group in 7 to set-up the desired Wittig coupling with the xanthone derived ylide 8.[3b] However, 7 proved too labile for meaningful chemical manipulations and the regioselectivity between the two benzylic position in it could not be achieved. Consequently, a strategy in which the A ring construction was deferred till the end was evolved.

Dimethyl homophthalate derivative **4b** was transformed to the aldehyde **10** through benzylic bromination to **9** and oxidation with bis-tetrabutylammonium dichromate.[7] Wittig reaction between **10** and the xanthone ylide **8**[3b] furnished the stilbene derivative **11a** in which the trans-isomer predominated. Sequential acylation and decarboxylation in the dicarboxylic acid **11b** led to the ketocarboxylic acid **12a**. As planned, the keto-acid **12a** underwent smooth lactonisation to the corresponding isocoumarin **13** on exposure to acetic anhydride and catalytic perchloric acid. Oxidative photocyclisation of **13** resulted in the generation of ring D and the hexacyclic isocoumarin **14**[4] was realised. The stage was set for the generation of ring A as demonstrated in Scheme 1; however, the desired reaction with 2-aminoethanol to furnish the cervinomycin framework could not be realised despite many trials and variations in reaction regimen. The only characterisable product from this reaction was the ring A secologue **15**[4] of cervinomycins, Scheme 2. An alternative route that met with success was, therefore, adopted. The keto-ester **12b** was photocyclised to the hexacyclic compound **16**[4] and this on treatment with 2-aminoethanol in methanol cyclised in the desired fashion, possibly through an intermediate 1,3-oxazolidine formation and intramolecular amidation, to furnish cervinomycin A_1 trimethyl ether **3**.[4,8] The trimethyl-ether **3** was elaborated in one step[9] to the cervinomycin-A_2 methyl ether **2b**, identical with the material prepared from **2a**.[10]



Scheme 1

Reagents & Yield: (i) Ac_2O, Py., 30°C, 10h, 73%; (ii) 10% aq. NaOH, , 1h; (iii) Ac_2O, $HClO_4$(Cat.), EtOAc, 30°C, 4h, 77% from **4a**; (iv) 2-aminoethanol, MeOH, 30°C, 12h, 50%; (v) N-bromosuccinimide, AIBN, CCl_4, , 2h, 60%; (vi) $[(n\text{-}C_4H_9)_4N]_2Cr_2O_7$, $CHCl_3$, , 2h, 80%.



Scheme 2

Reagents & Yield: (i) K_2CO_3, 18-crown-6, THF, 30°C, 8h, quant.; (ii) 20% aq.KOH, MeOH, , 4h, 90%; (iii) Ac_2O, DMAP, 30°C, quant.; (iv) 10% aq.NaOH, , 1h, quant.; (v) Ac_2O, $HClO_4$(Cat.), $CHCl_3$, 24h, 75%; (vi) hν, I_2, CH_2Cl_2, 10 min., 30%; (vii) 2-aminoethanol, CH_2Cl_2, 30°C, 36h; $BF_3.Et_2O$, CH_2Cl_2, 0°C, 70%; (viii) CH_2N_2, Et_2O/CH_2Cl_2, 10°C, 85%; (ix) hν, I_2, CH_2Cl_2, 25%; (x) 2-aminoethanol, MeOH, 30°C, 72h, 40%. (xi) AgO-6N HNO_3, dioxan, 70%.

References and Notes

1. Other member of the family include: (a) Lysolipin I, Dabler, M.; Keller-Schierlein, W. Helv. Chim. Acta, **1977**, 60, 178. (b) Albofungin and chloroalbofungin, Gurevich, A.I.; Karapetyan, M.G.; Kolosov, M.N.; Omelchenko, V.N.; Onoprienko, V.V.; Petrenko G.I.; Popravko, S.A.; Tetrahedron Lett., **1972**, 1751; Onoprienko, V.V.; Kozmin, Yu P.; Kolosov, M.N. Bioorg. Khim., **1978**, 4, 1418; Chem. Abstr., **1979**, 90, 54885 U. (c) Actinoplanones A-G, Kobayashi, K.; Nishino, C.; Ohya, J.; Sato, S.; Mikawa, T.; Shiobara, Y.; Kodama, M. J. Antibiot., **1988**, 41, 502 and 741. (d) Simaomicins α and β, Lee, T.M.; Carter, G.T.; Borders, D.B. J. Chem. Soc., Chem. Commun., **1989**, 1771.
2. (a) Omura, S.; Iwai, Y.; Hinotozawa, K.; Takahashi, Y.; Kato, J.; Nakagawa, A. J. Antibiot., **1982**, 35, 645. (b) Omura, S.; Nakagawa, A.; Kushida, K.; Lukacs, G. J. Am. Chem. Soc., **1986**, 108, 6088. (c) Nakagawa, A.; Omura, S.; Kushida, K.; Shimizu, H.; Luckacs, G. J. Antibiot., **1987**, 40, 301.
3. (a) Kelly, T.R.; Jagoe, C.T.; Li, Q. J. Am. Chem. Soc., **1989**, 111, 4522. (b) Mehta, G.; Venkateswarlu, Y. J. Chem. Soc., Chem. Commun., **1988**, 1200. (c) Rama Rao, A.V.; Reddy, K.K.; Yadav, J.S.; Singh, A.K. Tetrahedron Lett., **1988**, 3991. (d) For studies directed towards lysolipin I, see, Duthaler, R.O.; Heuberger, C.; Urs H.-U. Wegmann. Urs H.-U.; Scherrer, V. Chimia, 1985, 39, 174.
4. All new compounds reported here gave satisfactory spectral data and analytical or mass spectral data. **7**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (3H, s), 2.35 (3H, s), 2.93 (1H, d, J=14.6Hz), 3.08 (1H, d, J=14.6Hz, 3.55 (1H, m), 3.90 (3H, s), 4.00-4.20 (3H, m), 6.62 (1H, s), 6.70 (1H, s); m/z 247 (30%, M+), 162 (100%). **16**: ^{1}H NMR (100 MHz, $CDCl_3$): δ 2.24 (3H, s), 3.50 (3H, s), 3.65 (3H, s), 3.90 (2H, s), 3.98 (3H, s), 4.01 (3H, s), 4.03 (3H, s), 4.18 (3H, s), 7.00 (1H, s), 7.40 (1H, s), 7.62 (1H, d, J=8.5Hz), 7.66 (1H, s), 8.02 (1H, d, J=8.5Hz); m/z 560 (20%, M+), 529 (100%). **3**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (3H, s), 3.21 (1H, d, J=14.8Hz), 3.29 (1H, d, J=14.8Hz), 3.67-3.70 (1H, m masked by OCH_3 signals), 3.68 (3H, s), 3.70 (3H, s), 4.01 (3H, s), 4.06 (3H, s), 4.18 (3H, s), 4.16-4.24 (3H, m), 7.00 (1H, s), 7.32 (1H, s), 7.61 (1H, d, J=8.5Hz), 7.73 (1H, s), 8.05 (1H, d, J=8.5Hz); m/z 571 (25%, M+), 540 (100%).
5. Tamura, Y.; Fukata, F.; Tsugoshi, T.; Sasho, M.; Nakajima, Y.; Kita, Y. Chem. Pharm. Bull., **1984**, 32, 3259.
6. Tirodkar, R.B.; Usgaonkar, R.N. Ind. J. Chem., 1972, 10, 679; Modi, A.R.; Usgaonkar, R.N. ibid, 1979, 17b, 360.
7. Landini, D.; Rolla, F. Chem. Ind. (London), **1979**, 213.
8. Drs. A.V. Rama Rao, J.S. Yadav and colleagues at IICT, Hyderabad have independently synthesised cervinomycins following a different approach (accompanying communication). We thank them for helpful discussions and comparison of the ^{1}H NMR spectrum of 16.
9. Snyder, C.B.; Rapoport, H. J. Am. Chem. Soc., 1972, **94**, 227.
10. We thank Dr. Y. Venkateswarlu, who initiated this project, for his continued interest and help. This work was supported by UGC and CSIR.

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