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Total Syntheses of (±) Cervinomycins A_1 and A_2

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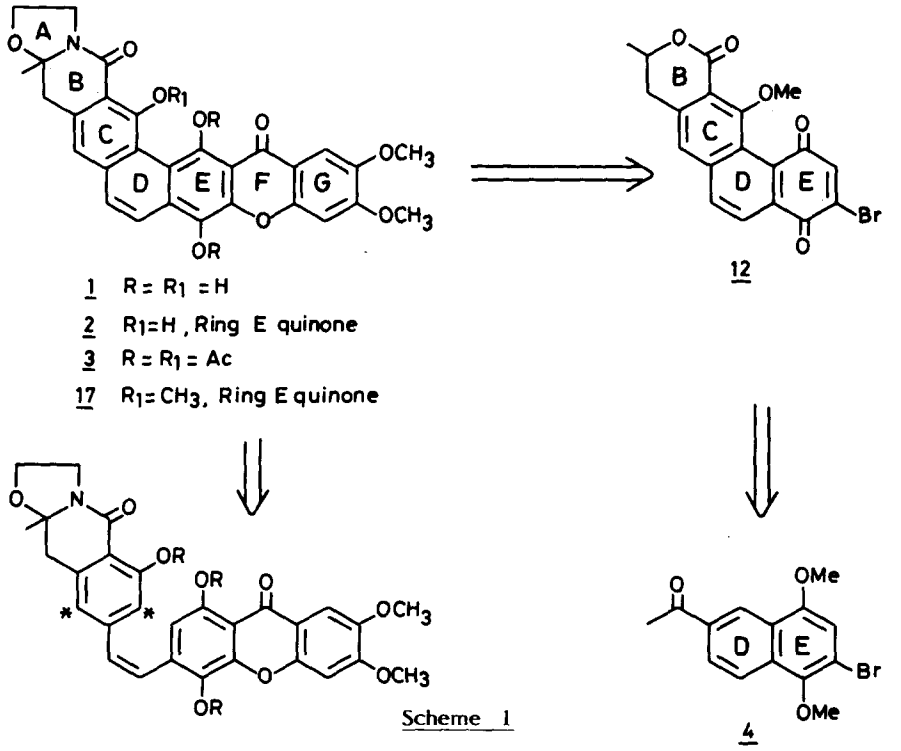
Abstract: Regiocontrolled total syntheses of cervinomycins A_1 (1) and A_2 (2) have been achieved from easily accessible 6-acetyl-2-bromo-1,4-dimethoxynaphthalene (4).

Cervinomycins[1] A_1 (1) and A_2 (2) belong to a small but growing family[2] of antibiotics, all of which possess xanthone and isoquinolone moieties juxtaposed angularly in a polycyclic aromatic framework. The triacetyl cervinomycin A_2 (3) is being developed[3] as a drug because of its potent antianaerobic activity against several bacteria. Owing to their skeletal novelty and potent activity, several groups[4,5] have attempted their syntheses. However only one total synthesis[6] has appeared so far. Herein, we report a regiocontrolled, elegant approach for the total syntheses of cervinomycins A_1 (1) and A_2 (2).

Our synthetic technology is based on the retrosynthetic protocol which dictates that we deviate from the bridging of isoquinolone (ABC fragment) and xanthone (EFG fragment) moieties by photocyclisation (Scheme I). This will not rule out the preferred[5a] possibility

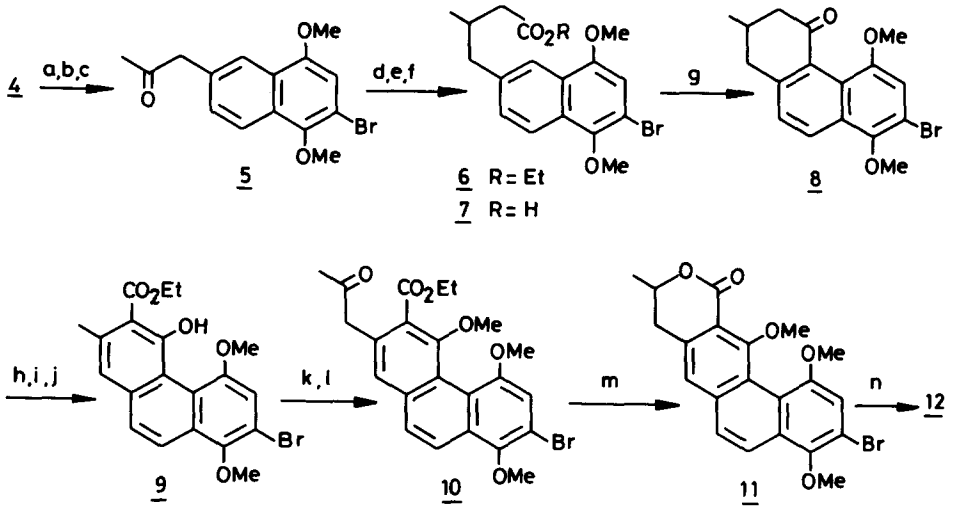


Scheme 1

of coupling at para to -OH group of the C ring. Hence our strategy centres around the key intermediate **4** constituting DE ring, which will allow us to regioselectively build the xanthone and isoquinolone moieties on it.

An expedient approach to the synthesis of key intermediate **12** with the BCDE ring unit, from 6-acetyl-2-bromo-1,4-dimethoxynaphthalene (**4**)[7] is illustrated in Scheme II. Our plan relies upon the strategically placed bromine and acetyl functionalities in **4** providing access to regiocontrolled introduction of xanthone and the C ring of cervinomycin respectively. Thus, compound **4** was first converted to 2-bromo-1,4-dimethoxy-6-naphthyl acetone **5** by a 3 step sequence. The ketone **5** was then olefinated with $Ph_3P{=}CHCO_2Et$ and the resulting cis/trans mixture was hydrogenated to provide the ester **6**. The ester **6** was hydrolysed to give the acid **7**, which on treatment with PPE furnished[9] the angular keto compound **8** as sole product. The ester functionality at the -position of the keto group was introduced by treatment of **8** with NaH/diethyl carbonate followed by aromatization of the C ring to produce the substituted phenanthrene **9**.

Scheme II



Reagents & Conditions:

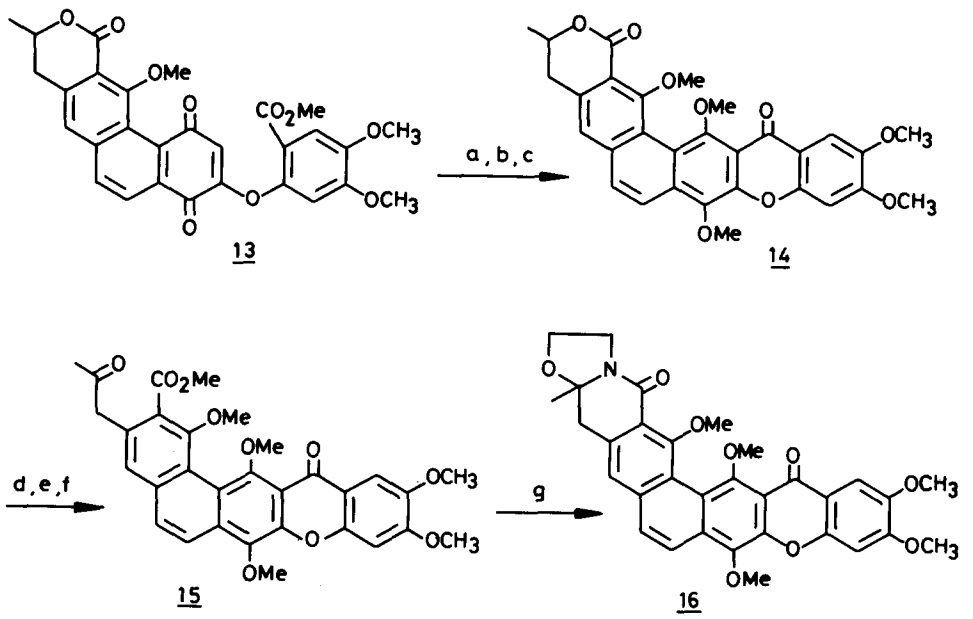
(a) Thallium(III)nitrate trihydrate[8] (1 eq), 2:2:1 MeOH:Dioxane:$HClO_4$, 0-25°C, 1 h, 85%; (b) aq.KOH (2 eq), MeOH, 25°C, 12 h, 98%; (c) 2.1 eq of MeLi in ether soln, 0-25°C, 1 h, 65%; (d) $Ph_3P{=}CHCO_2Et$ (2 eq), toluene, reflux, 36 h, 91% (e) H_2, PtO_2, EtOH, 1 atm; (f) KOH (2 eq), EtOH, 25°C, 8 h; (g) Excess PPE, $CHCl_3$, 25°C, 30 h, over all yield from **6** 52%; (h) NaH (2.1 eq), diethyl carbonate, THF, reflux, 16 h, 75%; (i) $C_5H_5NHBr_3$ (1 eq) AcOH, 25°C, 1 h, 95% (j) DBU (2 eq), CH_2Cl_2, 25°C, 10 h, 65%; (k) K_2CO_3 (3 eq), DMS (2 eq), acetone, reflux, 10 h, 85%; (l) LDA (2.5 eq), N-methoxy-N-methylacetamide (2.5 eq), THF, -78°C, 1.5 h, 74%; (m) $NaBH_4$ (0.5 eq), K_2CO_3 (1 eq), MeOH, 25°C, 30 min, 80%; (n) $(NH_4)_2Ce(NO_3)_6$ (2 eq), CH_3CN, H_2O, 25°C, 15 min, 95%.

We next turned our attention to elaborate **9** to the desired quinone **12**. Thus, the methyl ether of the **9** was converted to the keto compound **10** using N-methoxy-N-methylacetamide[10]. Reduction of the ketone **10** by $NaBH_4$ resulted in the formation of lactone **11**. As anticipated,

the displacement of the bromine in **11** by phenoxide ion proved difficult and hence lactone **11** was converted to the quinone **12** by oxidative demethylation[11].

With the key synthon **12** in hand, we then proceeded to build the xanthone unit by reacting quinone **12** with methyl 2-hydroxy-4,5-dimethoxybenzoate[12] in the presence of anhydrous K_2CO_3 in DMF. The resultant quinone **13** was then converted to the pentacyclic methyl ether **15** (Scheme III).

Scheme III

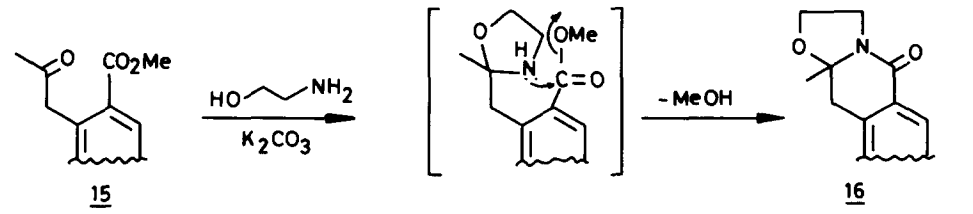


Reagents & Conditions:

(a) aq. $Na_2S_2O_4$; K_2CO_3 (5 eq), DMS (4 eq), acetone, reflux, 6 h; (b) aq. KOH (1.5 eq), EtOH, 25°C, 10 h; (c) Excess PPE[13], $CHCl_3$, 25°C, 36 h, over all yield from **13** 62%; (d) aq. KOH (1.5 eq), EtOH, 25°C, 8 h (e) CH_2N_2, ether; (f) PCC (1.2 eq), CH_2Cl_2, 25°C, 15 h, over all yield from **14** 90%; (g) $H_2NCH_2CH_2OH$ (2 eq), K_2CO_3 (1.5 eq), MeOH, 25°C, 36 h, 82%.

We then addressed the key annulation of the oxazolidine ring to give the final skeleton which proved to be more difficult than anticipated. Our earlier experience[4] to form oxazolidine ring on isocoumarin which often furnished side product in a varied amount, was also substantiated by Kelly[6]. This prompted us to look for an alternative method. The mechanism of the

Scheme IV



reaction came as a redressal to choose methyl keto ester as depicted in the Scheme IV as requisite precursor for building oxazolidine ring. Hence, our attempt on methyl keto ester **15** with ethanolamine which involves initial protection of keto group[14] and subsequent intramolecular amidation onto ester, turned out to be successful, furnishing the desired oxazolidine **16.**

As a final step, chemoselective oxidative demethylation[11] of E ring in **16** was achieved by ceric ammonium nitrate/aq. CH_3CN to give **17** in 95% yield. After several unsuccessful attempts, $Et_3N{:}BCl_3$ (in dichloromethane, at 0°C 15 min, 85%) was found to be an optimum reagent[15] for deprotecting the methoxyl group of ring C, thereby furnishing cervinomycin-A_2 (2). This, on reduction with $NaBH_4$ yielded cervinomycin A_1 (1). The NMR and IR spectra of these synthetic materials were superimposable with those of natural cervinomycins[16].

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12. Prepared from Asaranaldehyde (Fluka) by oxidation ($NaClO_2$, NH_2SO_3H), esterification (CH_2N_2) and selective mono demethylation to obtain the product in 65% yield.
13. For similar cyclisation with PPA, see: G. Metz, Synthesis, 1972, 612.
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15. Prepared by addition of BCl_3 (1 eq) in CH_2Cl_2 containing Et_3N (1.1 eq).
16. Prof G Mehta and Mr S R Shah have independently synthesised compound 15 by a different strategy and converted to Cervinomycin trimethyl ether by our approach.

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