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Total Synthesis of Novel Xanthone Antibiotics (±)-Cervinomycins A_1 and A_2

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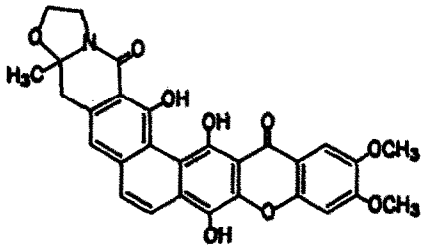
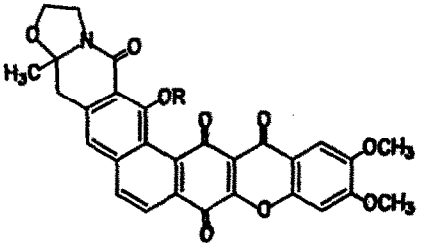
Abstract: A total synthesis of novel heptacyclic antibiotics cervinomycin A_1 1 and A_2 2 following a convergent approach is reported. The cornerstone of our strategy was the construction of the central ring D through photochemical electrocyclization. The oxazolo-isoquinolinone fragment (ABC rings) 7 and the xanthone fragment (EFG rings) 8 were assembled through relatively straightforward synthetic protocols and coupled through a Wittig reaction to give 6 and set upthe key photocyclization. Our successful approach to 1 and 2 can be readily adapted to the synthesis of analogues of these interesting antibiotics.

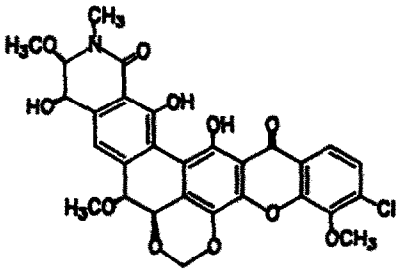
The genus streptomyces is a prodigious source of structurally variegated and biologically potent metabolites.[1] A new species Streptomycis cervinus sp.nov. in this genus was recently discovered and a collaborative effort led to the isolation and structure determination of novel antibiotic substances cervinomycins A_1 1 and A_2 2 in 1986.[2] These compounds



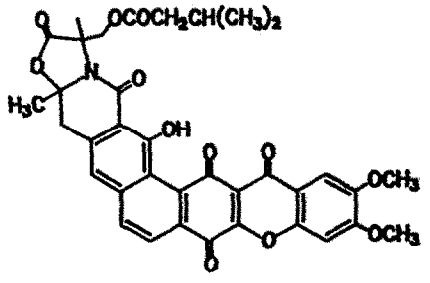
Cervinomycin A_1 1



Cervinomycin A_2 2



Lysolipin I 3



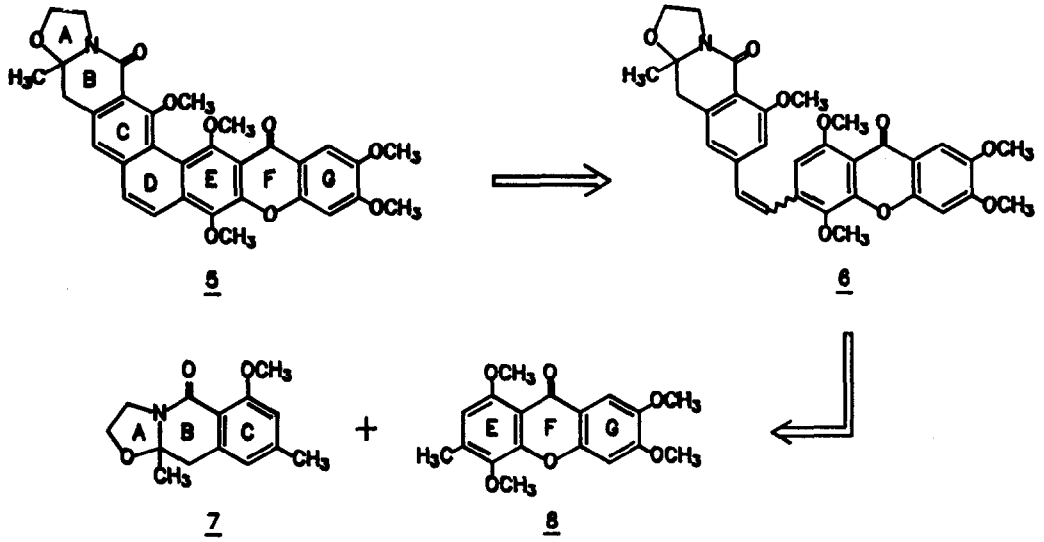
Citreamicin α 4

closely related as a redox pair, attracted immediate attention on account of their promising activity against anaerobic bacteria, mycoplasma and some gram positive bacteria and their structural novelty.

The cervinomycins A_1 and A_2 belong to a small but esoteric group of antibotics embodying an angularly fused polycyclic framework in which xanthone and isoquinolinone moieties are readily discernible.[3] Some other members of this group that have been characterized are lysolipin 3[3b] and citreamicin 4.[3e] The lure of novel structural features present in 1-4 and their promising biological profile has generated considerable synthetic interest in these compounds. Initial model studies[4] towards their synthesis have been followed by the first total synthesis of cervinomycin in 1989.[5] Subsequently, two more total syntheses by us[6a] and others,[6b] following different strategies, have been reported. In addition, some more model studies have also been reported, indicating continued synthetic interest in these molecules.[6c,d] We describe herein full details of our synthesis of 1 and 2 following a short convergent strategy.[7]

Synthetic Strategy

We conceived a synthetic approach to the heptacyclic framework of 1 and 2 through the protected derivative 5 which could be assembled through the union of two preformed ABC and EFG fragments 7 and 8, respectively. The retrosynthetic analysis (Scheme 1), indicated the synthetic plan that required parallel synthesis of the oxazolo-isoquinolinone 7 and the penta-substituted xanthone 8 parts and their coupling to set up the formation of the strained ring D *via* photocyclization in 6. Interestingly, this



5 6

7 8

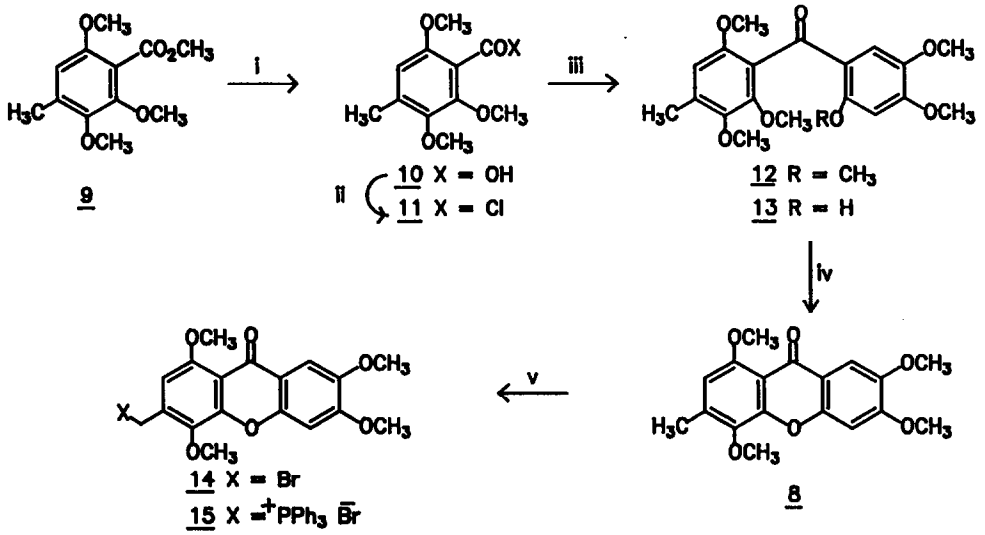
Scheme 1

strategy is not only economical and conceptually appealing but requires that the dense functionalization of 1 and 2 is built separately in fragments ABC and EFG and the cumbersome D ring, providing the angular fusion,

is generated only towards the end. For the coupling of ABC and EFG components to access the precursor 6 for photocyclization, Wittig reaction appeared most appropriate and complementary functionalization for this purpose was sought to be created through the benzylic methyl groups in 7 and 8.

Synthesis of the EFG Ring Fragment

While the number of synthetic and natural xanthones abound in the literature, none having the substitution pattern present in the EFG fragment 8 with a methyl group at the desired position has been reported. From the available options for the construction of 8, it was considered most convenient to access the xanthone framework via a base catalyzed cyclization of the corresponding benzophenone 13. A synthesis of 13 from readily available starting materials and reagents is depicted in Scheme 2. The



Scheme 2

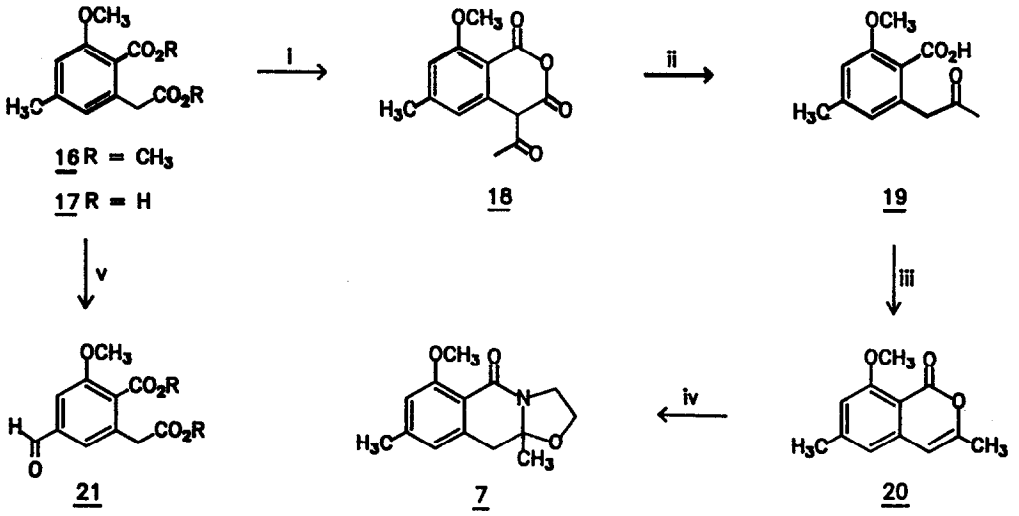
Reagents & Conditions: (i) 10% aq.KOH, CH_3OH, reflux, 4h, 95%; (ii) $SOCl_2$, reflux, 2h; (iii) 1,2,4-trimethoxybenzene, ether, anh.$AlCl_3$, r.t., 12h; (iv) CH_3OH, aq.K_2CO_3, reflux, 12h, 70%, (v) NBS, AIBN, CCl_4, reflux, 3h, 80%.

starting 2,3,6-trimethoxy-p-toluic acid methyl ester is available from orcinol in five straightforward steps,[8] which were slightly modified to suit our requirements. The ester 9 was hydrolyzed to give the acid 10 which was further transformed to the acid chloride 11. The acid chloride 11 was used to acylate 1,2,4-trimethoxybenzene in the presence of anhydrous $AlCl_3$ to furnish a mixture of hexamethoxybenzophenone 12 and its mono-demethylated derivative 13 in varying ratios depending upon the amount of the catalyst used and the time given.[9] While 12 and 13 could be separated, in practice it was more convenient to subject the mixture to base catalyzed cyclization to yield xanthone 8 in good yield. The benzo-

phenone 12 could be recovered unchanged from the reaction and could be recyclized via $AlCl_3$ mediated demethylation to 13. The methyl group in xanthone 8 could be readily activated through benzylic bromination with N-bromosuccinimide (NBS) to furnish 14. The bromomethyl group in 14 was then transformed to the required triphenylphosphonium bromide 15, Scheme 2, the Wittig component for the contemplated coupling with the ABC fragment as per the retrosynthetic protocols shown in Scheme 1.

Synthesis of the ABC Ring Fragment

For the synthesis of the ABC portion of the cervinomycins, we chose to employ 3-methoxy-5-methylhomophthalic acid 17,[10] readily obtainable in gram quantities from the Diels-Alder reaction between 6-methoxy4-methyl-2-pyrone and 1,3-dicarbomethoxyallene and hydrolysis of the resulting ester 16. The acid 17 was converted[11] to isochroman-1,3-dione derivative 18 with Ac_2O-pyridine and further decarboxylated with aqueous base to give 2-acetylmethyl-6-methoxy-4-methylbenzoic acid 19. Cyclization of 19 in the presence of Ac_2O and cat.$HClO_4$[12] gave 3,6-dimethyl-8-methoxyisocoumarin 20. Treatment of 20 with 2-aminoethanol led to the oxazolo-isoquinolinone 7 with a quaternary methyl group at the ring junction in 50% yield, Scheme 3. Acquisition of the ABC fragment was revealed by its distinctive ^1H NMR spectrum (δ 1.27, 3H, s; 2.93, 1H, d and 3.08 1H, d).



Scheme 3

Reagents & Conditions: (i) Ac_2O, Py, 73% (ii) 10% aq.NaOH, ; (iii) Ac_2O, cat.$HClO_4$ 77%; (iv) 2-aminoethanol, CH_3OH, 50%; (v) NBS-CCl_4, $[N(n\text{-}Bu)_4]_2Cr_2O_7$-$CHCl_3$, 50%.

While the smooth attainment of 7 was gratifying, it was crucial at this stage to functionalize the benzylic methyl group present in 7 to enable its coupling with the ylide derived from 8. However, the attempts to functionalize 7 with NBS, SeO_2, etc. at the methyl group proved troublesome as regioselectivity between the two benzylic positions in 7

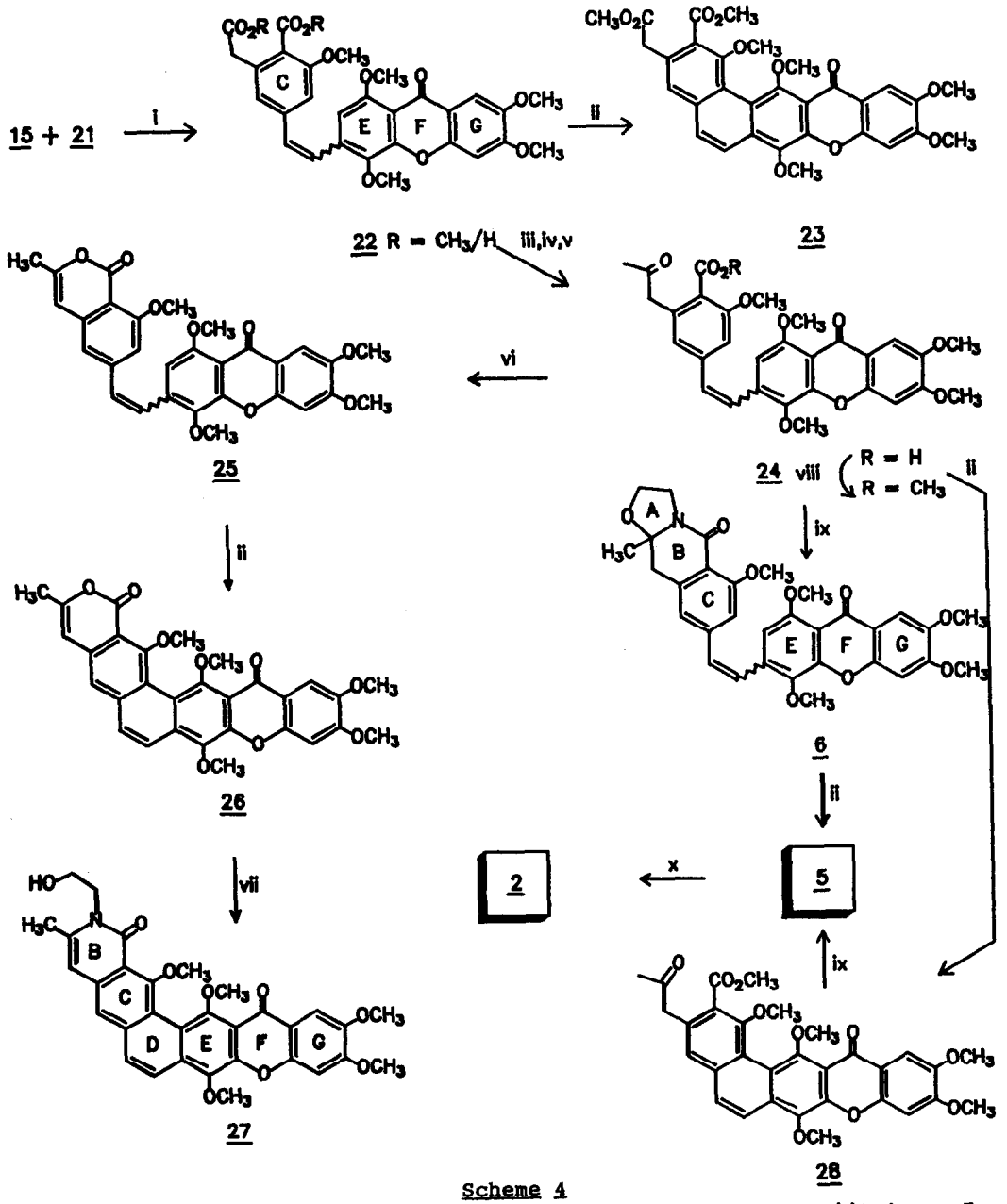
could not be achieved. We, therefore, sought to revert to functionalizing the benzylic methyl group in 20. However, 20 also exhibited undesired regioselectivity and, on reaction with NBS, only allylic bromination was observed. These difficulties necessitated recourse to some tactical modifications and the successful strategy that emerged is as below.

Elaboration to Cervinomycins A_1 1 and A_2 2

Since it became difficult to prepare appropriately functionalized derivative of 7 for the ABC + EFG coupling, we sought to deploy a suitable C ring precursor endowed with a functionalized methyl group for the Wittig coupling with the EFG fragment 15. In this tactical manoeuvre, the construction of the rings A and B needed to be deferred till the end stage of the synthesis. Thus, the dimethylhomophthalate derivative 16 was converted to the bromomethyl derivative regioselectivley and was further oxidized to the aldehyde 21 using bis-tetrabutylammonium dichromate[13] in good yield. The aldehyde 21 was then subjected to the Wittig reaction with the phosphonium ylide 15 derived from 14 in the presence of potassium carbonate as a base and 18-crown-6 as a PTC to furnish the coupled product 22, Scheme 4. The ^1H NMR spectral data for 22 showed it to be a mixture of E,Z-isomers but it was not considered necessary to separate them at this stage and the mixture was as such irradiated from a 450 W Hg lamp to furnish 23 in 20% yield. While the formation of CDEFG ring system 23 in a regioselective manner was a satisfying outcome and fortified our confidence in the overall synthetic plan, the yield was quite unacceptable for completing the rest of the synthesis which required elaboration of functionalities to install AB rings. Consequently, it was decided that the oxazolo-isoquinolinone moiety be constructed prior to the photocylization step.

The Wittig product 22 was subjected to a three step sequence similar to that outlined in Scheme 3, to furnish the homologated keto acid 24 (R=H) which was characterized as the corresponding methyl ester. The acid 24 on treatment with acetic anhydride and $HClO_4$ (cat.) delivered the isocoumarin 25 in a good yield. The presence of vinylic methyl resonance at δ 2.25 was fully supportive of the formation of 25. The isocoumarin 25 on irradiation in the presence of iodine lead to the hexacyclic isocoumarin 26, in better yield than was observed for the photocyclization of the homophthalate 22. At this stage, the final formation of the AB rings was just a step away as demonstrated in the model studies (Scheme 3, 20 $\longrightarrow$ 7). However, construction of the AB rings in 26 proved to be elusive and resulted only in the formation of the hexacyclic ring A secologue 27 of cervinomycin on reaction with 2-aminoethanol. Formation of 27 can be rationalized as shown in Scheme 5. Similar difficulties have been encountered previously.[5] However, as to why 20 and 26 exhibit this difference in reactivity is not quite clear.

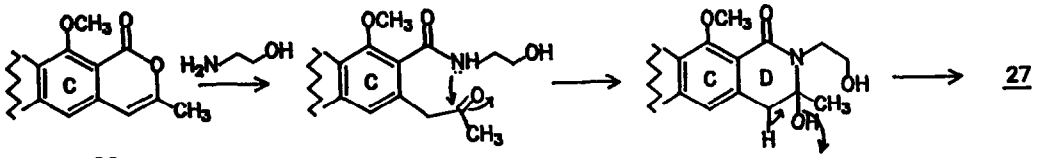
A search for the redressal of this unexpected hurdle at the threshold of our target made us to turn back and look at the precursor keto ester 24 (R=CH_3), which too can lead to the target compound on treatment with 2-aminoethanol through a double cyclization sequence.[6] Thus, the E,Z-mixture of the keto ester 24 was reacted with 2-aminoethanol and the oxazolo-isoquinolinone moiety was formed quite uneventfully as revealed by the appea-



Scheme 4

Reagents & Conditions: (i) K_2CO_3, 18-crown-6, THF, 90%; (ii) hν, I_2, CH_2Cl_2, 20-30%; (iii) 20% aq.KOH, CH_3OH, 90%; (iv) Ac_2O, DMAP, quant.; (v) 10% aq.NaOH, quant.; (vi) Ac_2O, $HClO_4$, $CHCl_3$, 75%; (vii) (a) 2-aminoethanol, CH_3OH; (b) $BF_3.Et_2O$, CH_2Cl_2, 70%; (viii) CH_2N_2, Et_2O/CH_2Cl_2, 85%; (ix) 2-aminoethanol, $MeOH/CH_2Cl_2$, 40-60%; (x) Ag_2O, 6N HNO_3, dioxan, 67%.

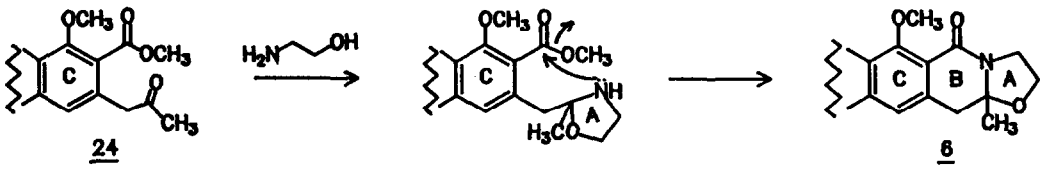
rance of the expected quarternary methyl singlet and benzylic methylene resonances in the ^1H NMR spectrum of 6. Formation of 6 from 24 can be rationalized as shown in Scheme 6. The resulting ABC_DEFG precursor 6 on short exposure to pyrex filtered UV irradiation in the presence of a catalytic amount of iodine delivered cervinomycin A_1 trimethyl ether 5. Alternatively, 5 could also be accessed from 24 via first photocyclization to 28 followed by the treatment with 2-aminoethanol.



26

Scheme 5

Cervinomycin A_1 trimethyl ether 5 was easily converted to cervinomycin A_2 methyl ether 2 (R=CH_3) through oxidation with either silver oxide or ceric ammonium nitrate[14] under carefully controlled conditions. The spectral data for cervinomycin A_2 methyl ether 2 was found to be identical with that reported in the literature.[2c] The monomethyl ether 2 has already been converted to 2 (R=H) and 1.[6b,5] The present work, therefore, constitutes a total synthesis of cervinomycin A_1 and A_2.



24 6

Scheme 6

Experimental

Melting points were recorded on a Buchi SMP-20 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1310 spectrophotometer and were calibrated against the polystyrene absorption at 1601 cm^{-1}. Solid samples were recorded as KBr wafers. ^1H NMR (100 MHz) and ^{13}C NMR (25 MHz) spectra were recorded on a JEOL FX 100 spectrometer unless and otherwise specified. NMR samples were dissolved in $CHCl_3$-d solvent and chemical shifts are reported in δ scale relative to tetramethylsilane as the internal standard. Elemental analyses were performed on a Perkin-Elmer 240C CHN analyser. Reactions were monitored by TLC employing appropriate solvent systems. Moisture sensitive reactions were carried out by using the standard syringe-septum technique. Solvents for reactions were dried over appropriate drying agents. Usual work-up procedure includes washing of solvent extracts with water and brine, drying over anhydrous Na_2SO_4 and concentration at reduced pressure on a Buchi RE-121 rotary evaporator. Yields reported are isolated yields of homogeneous material judged by TLC and NMR spectroscopy. All irradiations were carried out using 450 W medium

pressure Hanovia Hg immersion lamp.

2,3,6-Trimethoxy-p-toluic acid methyl ester 9

2,3,6-Trihydroxy-p-toluic acid methyl ester[8] (1.0g, 5 mmol) was dissolved in dry acetone (50 ml) to which anhydrous K_2CO_3 (5g, 36 mmol) and methyl iodide (7.0g, 50 mmol) were added and the resulting mixture was refluxed for 24h. The solvent was removed and the residue was diluted with water. Usual work-up with ether (3 x 50 ml) and concentration of the extracts gave the residue which was purified over SiO_2-gel column using 15% ethyl acetate/hexane mixture to yield 9 (1.06g, 88%); IR (neat): 1730, 1600, 1275, 1235, 1205 cm^{-1}; ^1H NMR: δ 6.44 (1H, s), 3.90 (3H, s), 3.88 (3H, s), 3.76 (6H, s), 2.26 (3H, s); Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.34; H, 6.67.

3-Methyl-1,4,6,7-tetramethoxyxanthone 8

To a solution of 9 (1.06g, 4.4 mmol) in CH_3OH (10 ml), 10% aqueous KOH solution (10 ml) was added and the mixture was refluxed with stirring for 4h. Methanol was removed under reduced pressure and contents were diluted with water and acidified (pH1) with dil.HCl. Extraction with ethyl acetate (3 x 20 ml) and removal of solvent gave 2,3,6-trimethoxy-4-methyl benzoic acid (0.95g, 95%); m.p. 154°C; IR (KBr): 2850(br), 1690, 1590, 1400, 1100, 920 cm^{-1}. The acid was refluxed with excess of thionyl chloride (10 ml) for 2h and excess thionyl chloride and HCl were completely removed under vacuum. The formation of 3,6-trimethoxy-4-methylbenzoyl chloride 11 was confirmed by IR (neat): 1780(s), 1600, 1120, 790 cm^{-1}. The acid chloride 11 was transferred using dry ether (15 ml) to a two necked RB flask containing 1,2,4-trimethoxybenzene (0.775g, 4.6 mmol) in dry ether (15 ml). To this mixture, anhydrous $AlCl_3$ (1.5g, 11 mmol) was added portion wise during 30 min. with the help of a solid addition funnel with stirring. The resulting solution was stirred at room temp. for 18h and poured onto crushed ice containing dil. HCl. Usual workup with ether and removal of solvent left a residue containing 2,3,6,2',4',5'-hexamethoxy-4-methylbenzophenone 12 and its monodemethylated derivative 13. These were separated through SiO_2-gel chromatography and characterized. 12: IR (neat): 1730, 1620, 1400, 1030 cm^{-1}; ^1H NMR: δ 2.28 (3H, s), 3.59 (3H, s), 3.63 (3H, s), 3.72 (3H, s), 3.78 (3H, s), 3.85 (3H, s), 3.92 (3H, s), 6.42 (1H, s), 6.44 (1H, s), 7.42 (1H, s). 13: IR (neat): 3300, 1730, 1600, 1220, 1040 cm^{-1}; ^1H NMR: δ 2.32 (3H, s), 3.47 (3H, s), 3.69 (3H, s), 3.85 (6H, s), 3.94 (3H, s), 6.08 (1H, s), 6.47 (1H, s), 6.92 (1H, s), 12.08 (1H, s).

The mixture of benzophenones 12 and 13 was dissolved in CH_3OH (20 ml) and potassium carbonate (5g) in water (45 ml) was added. The resulting mixture was refluxed overnight. Usual work-up with $CHCl_3$ (3 x 50 ml) gave a residue which was chromatographed on SiO_2-gel using 80% ethyl acetate/-hexane mixture to give the xanthone 8 (0.78g, 56%). The recovered benzophenone 12 was treated with anhydrous $AlCl_3$ in dry ether to demethylate a methoxy group on the ortho positions and repetition of the base catalyzed cyclization as described above gave an additional amount of 8 (0.2g), bringing the overall yield to 70%; m.p. 167-168°C; IR (KBr): 1650, 1620,

1600, 1490, 1270, 1120, 780 cm^{-1}; ^1H NMR: δ 2.42 (3H, s), 3.92 (3H, s), 3.97 (6H, s), 4.0 (3H, s), 6.56 (1H, s), 6.92 (1H, s), 7.62 (1H, s); ^{13}C NMR: δ16.35, 56.0, 56.12(2C), 60.83, 99.12, 105.40, 106.71, 111.12, 115.66, 137.36, 139.66, 146.6, 150.60, 151.00, 154.60, 155.48, 175.07. Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49. Found : C, 65.48; H, 5.50.

3-Bromomethyl-1,4,6,7-tetramethoxyxanthone 14

A mixture of 3-methyl-1,4,6,7-tetramethoxyxanthone 8 (0.25g, 0.75 mmol), CCl_4 (8 ml), NBS (0.15g, 0.87 mmol) and azobisisobutyronitrile (AIBN, 0.02g) was refluxed under N_2 for 3h. The reaction mixture was concentrated and the residue chromatographed on SiO_2-gel using 70% ethyl acetate/hexane as an eluent to give 14 (0.248g, 80%); m.p. 206-208°C; IR (KBr): 1660, 1620, 1600, 1480, 1280, 780 cm^{-1}; ^1H NMR: δ 3.96 (3H, s), 3.98 (3H, s), 4.01 (3H, s), 4.08 (3H, s), 4.6 (2H, s), 6.72 (1H, s), 6.82 (1H, s), 7.6 (1H, s); ^{13}C NMR: δ 26.65, 56.18, 56.42(2C), 61.77, 99.12, 105.54, 105.95, 113.12, 115.9, 136.13, 139.95, 147.0, 150.66, 155.07, 155.94, 174.95. Anal. Calcd. for $C_{18}H_{17}BrO_6$: C, 52.86; H, 4.19). Found: C, 52.90; H, 4.16.

1,4,6,7-Tetramethoxyxanthon-3-ylmethyltriphenylphosphonium bromide 15

A mixture of triphenylphosphine (0.24g, 0.9 mmol) and the bromomethyl xanthone 14 (0.25g, 0.6 mmol) in toluene (10 ml) was refluxed with stirring for 5h and allowed to cool to room temp. The precipitated phosphonium salt was filtered and washed with toluene (5 ml) and dried under vacuum to yield 15 (0.33g, 81%), m.p. 223-4°C.

3,6-Dimethyl-8-methoxyisocoumarin 20

To a well stirred mixture of acetic anhydride (1.5 ml) and dry pyridine (0.25 ml), 3-methoxy-5-methyl homophthalic acid[10] 17 (0.186g, 0.83 mmol) was added in small portions at room temp. and stirring was continued for 2h during which dry ether (5 ml) was added to facilitate smooth stirring. The solid product was filtered, washed with ether and dried under vacuum to give the intermediate 4-acetyl-8-methoxy-6-methyl-isochroman-1,3-dione 18 (0.15g, 73%) m.p. 182°C(d); IR (KBr): 1745, 1640, 1560, 1200, 1000, 840 cm^{-1}; ^1H NMR: δ 2.44 (3H, s), 2.56 (3H, s), 3.96 (3H, s), 6.68 (1H, s), 6.82 (1H, s).

To a stirred suspension of 18 (0.15g, 0.6 mmol) in water (1 ml) was added an aq. solution of sodium hydroxide (10%, 2 ml) and the resulting mixture was heated on a steam bath for 2h., cooled to room temp. and acidified with HCl to pH 1. Extraction with ethyl acetate (3x 7 ml) and addition of acetic anhydride (1 ml) and 70% perchloric acid (1 drop) resulted in a dark solution which was stirred under N_2 for 4h. The reaction was quenched with aq.$NaHCO_3$ and usual work-up gave a residue which was chromatographed using SiO_2-gel with 40% ethyl acetate/hexane as an eluent to give 3,6-dimethyl-8-methoxyisocoumarin 20 (0.95g, 77%) m.p. 137°C, IR (KBr): 1720, 1650, 1600, 1320, 1240, 1030, 960 cm^{-1}; ^1H NMR: δ 2.21 (3H, d, J=1Hz), 2.41 (3H, s), 3.96 (3H, s), 6.06 (1H, d, J=1Hz), 6.66 (2H, br s); ^{13}C NMR: δ 19.12, 21.94, 55.89, 103.30, 106.18, 110.36, 117.19, 140.36, 146.95, 154.84, 159.65, 161.36. Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found : C, 70.45; H, 5.90.

2,3,10,10a-Tetrahydro-8,10a-dimethyl-6-methoxyoxazolo[3.2-b]isoquinolin-5-one 7

To a solution of 3,6-dimethyl-8-methoxyisocoumarin 20 (0.02g, 0.098 mmol) in CH_3OH (0.1 ml) was added 2-aminoethanol (0.1 ml) in CH_3OH and the mixture was stirred for 12h at room temp. Removal of solvent and chromatography on SiO_2-gel using ethyl acetate as an eluent afforded 7 (0.012g, 50%); m.p. 113°C, IR (KBr): 1655, 1610, 1310, 1100, 840 cm^{-1}; ^1H NMR: δ (500 MHz) 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), 4.0-4.2 (3H, m), 6.62 (1H, s), 6.7 (1H, s); LRMS: m/z = 247 (M^+, 30%), 162 (100%); Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.06 ; H, 6.95. N, 5.70.

Dimethyl-5-formyl-3-methoxyhomophthalate 21

Dimethyl-3-methoxy-5-methylhomophthalate[10] 16 (0.55g, 2.2 mmol), NBS (0.466g, 2.6 mmol) and AIBN (0.03g) in CCl_4 (10 ml) were refluxed under N_2 for 2h. Succinimide separated and was filtered and the residue after removal of solvent was chromatographed over SiO_2-gel column using 20% ethyl acetate/hexane as an eluent to give dimethyl-5-bromomethyl-3-methoxyhomophthalate (0.43g, 60%), m.p.88°C; IR (KBr): 2950, 1730, 1610, 1580, 1430, 1310, 1225, 1100 cm^{-1}; ^1H NMR: δ 3.64 (2H, s), 3.68 (3H, s), 3.85 (3H, s), 3.88 (3H, s), 4.44 (2H, s), 6.90 (2H, s); δ 32.24, 38.30, 51.59, 51.71, 55.59, 110.71, 123.07, 123.19, 133.42, 140.48, 156.95, 167.07, 170.48. Anal. Calcd. for $C_{13}H_{15}BrO_5$: C, 47.14; H, 4.57. Found: C, 47.41; H, 4.64.

The bromomethylhomophthalate (0.34g, 1.03 mmol) and bis-tetrabutylammoniumdichromate[14] (1.5g, 2.07 mmol) were dissolved in $CHCl_3$ (7.0 ml) and the resulting solution was refluxed for 2h under N_2. The reaction mixture was filtered through florisil (60 mesh) and washed with ether. Combined organic washings were concentrated and the residue was chromatographed over SiO_2-gel employing 25% ethyl acetate/hexane to yield 21 (0.228g, 83%); m.p. 76°C; IR (KBr): 1720, 1695, 1590, 1460, 1280, 1220, 1100 cm^{-1}; ^1H NMR: δ 3.64 (2H, s), 3.65 (3H, s), 3.90 (3H, s), 3.92 (3H, s), 6.36 (1H, s), 6.37 (1H, s), 9.96 (1H, s); ^{13}C NMR: δ 38.1, 51.83, 52.12, 55.89, 108.83, 125.54, 128.77, 133.9, 137.99, 157.30, 166.70, 170.30, 191.19; Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30 . Found: C, 58.72; H, 5.29.

(E,Z)-Dimethyl-5[(1,4,6,7-tetramethoxyxanthone-3-yl)ethen-2-yl]-3-methoxyhomophthalate 22

In a two necked RB flask were placed the Wittig salt 15 (0.225g, 0.33 mmol), anhydrous potassium carbonate (0.15g), 18-crown-6 (0.01g) and dry tetrahydrofuran (5 ml) and the suspension was stirred for 1h under N_2. To the resulting dark yellow solution, aldehyde 21 (0.098g, 0.369 mmol) in tetrahydrofuran (3 ml) was added dropwise. The reaction mixture was stirred at room temp. overnight and after the usual workup with CH_2Cl_2 furnished a residue which was purified by hydrolysis to the corresponding acid and re-esterification with diazomethane to give 22 (0.175g, 90%) as a mixture of E,Z-isomers; IR (KBr): 1735, 1620, 1600, 1470, 1425, 1290, 1120 cm^{-1}; ^1H NMR: δ 3.50-4.1 (m), 6.48(s), 6.7-7.64 (m); Anal. Calcd. for

$C_{31}H_{30}O_{11}$: C, 64.35; H, 5.23. Found: C, 64.36; H, 5.23.

1,7,10,11,14-Pentamethoxy-3-(Methoxycarbonylmethyl)naphtho[1,2-b]-xanthone-2-carboxylic acid methyl ester 23

The xanthone diester 22 (20 mg, 0.034 mmol) was irradiated in CH_2Cl_2 (40 ml) containing a catalytic amount of I_2 in a quartz vessel for 10 min. The solvent was removed and the residue was chromatographed on SiO_2-gel column using 1:1:1, $CHCl_3$:ethylacetate:hexane mixture as an eluent to furnish the pentacyclic diester 23 (4.0 mg, 20%); m.p. 206-209°C; IR (KBr): 1730, 1600, 1420, 1270, 1100 cm^{-1}; ^1H NMR: δ 3.48 (3H, s), 3.64 (3H, s), 3.72 (3H, s), 3.84 (2H, s), 3.96 (3H, s), 4.0 (3H, s), 4.04 (3H, s), 4.16 (3H, s), 7.00 (1H, s), 7.50 (1H, s), 7.66 (1H, d, J=9Hz), 7.72 (1H, s), 8.04 (1H, d, J=9Hz); [HRMS: M^+ Calcd. for $C_{31}H_{28}O_{11}$: 576.1631. Found: 576.1661].

(E,Z)-3-Methyl-8-methoxy-6-[(1,4,6,7-tetramethoxyxanthon-3-yl)ethen-2-yl]isocoumarin 25

The diester 22 (0.163g, 0.28 mmol) in methanol (5 ml) was hydrolyzed to the corresponding homophthalic acid by refluxing with aq.KOH (10%, 5 ml) for 4h. Removal of methanol and acidification with HCl gave the homophthalic acid 22 (R=H) (0.115g, 0.28 mmol); IR (KBr): 3400, 1720, 1620, 1480, 1290 cm^{-1}. To a mixture of acetic anhydride (1 ml) and 4-dimethylaminopyridine (0.06g) was added homophthalic acid derivative 22 (0.155g, 0.28 mmol) and the mixture was stirred overnight at room temp. The yellow precipitates that separated were filtered and washed with ether and dried to give isochroman-1,3-dione derivative (0.16g, quantitative); IR (KBr): 1700, 1640, 1620, 1590, 1480 cm^{-1}. The above derivative was suspended in water (1 ml) and sodium hydroxide solution (10%, 2 ml) was added with stirring. The mixture was heated at 110°C for 2h and acidified to pH 1 with HCl. The precipitated product was filtered, washed with water (15 ml) and dried to give the keto acid 24 (R=H) (0.145g, 95%); IR (KBr): 1720, 1620, 1600, 1490, 1290, 1220, 1120 cm^{-1}.

To a stirred solution of the keto acid 24 (0.145g, 0.265 mmol) in $CHCl_3$ (30 ml) was added acetic anhydride (1.0 ml) followed by 70% perchloric acid (2 drops). Stirring was continued for 24h at room temp. and the solvent was removed. Addition of saturated $NaHCO_3$ (10 ml), extraction with CH_2Cl_2, usual work-up and removal of solvent gave a residue which was chromatographed on SiO_2-gel column using 2% $CH_3OH/CHCl_3$ to afford 25 (0.105g, 75%). Recrystallization furnished the major (E)-isomer, m.p. > 275; IR (KBr): 1740, 1650, 1620, 1600, 1470, 1220, 1200, 1120 cm^{-1}; ^1H NMR: δ 2.26 (3H, s), 3.98 (3H, s), 4.04 (6H, s), 4.07 (3H, s), 4.09 (3H, s), 6.18 (1H, s), 6.94 (2H, s), 7.04 (2H, br s), 7.22 (1H, d, J=16Hz), 7.62 (1H, d, J=16Hz), 7.64 (1H, s).

8,11,12,15,16-Pentamethoxy-3-methyl-isocoumarino[7,6-a]benzo[6,5-b]-xanthone 26

The diastereomeric mixture of isocoumarin-xanthone 25 (60 mg, 0.11 mmol) in CH_2Cl_2 (100 ml) containing catalytic amount of iodine was photolyzed in a quartz tube for 10 min. Solvent was removed and the residue was chromatographed over SiO_2-gel using 1:1:1

$CHCl_3$:ethylacetate:hexane solvent mixture as an eluent to give hexacyclic isocoumarin derivative 26 (20 mg, 33%); m.p. 190°C; IR (KBr): 1720, 1650, 1580, 1470, 1450, 1270, 1110, 1040 cm^{-1}; ^1H NMR: δ 2.26 (3H, d, J=1Hz), 3.40 (3H, s), 4.00 (3H, s), 4.06 (3H, s), 4.14 (3H, s), 4.20 (3H, s), 6.56 (1H, d, J=1Hz), 6.99 (1H, s), 7.16 (1H, s), 7.64 (1H, d, J=9Hz), 7.70 (1H, s), 8.18 (1H, d, J=9Hz); ^{13}C NMR: δ (50 MHz) 19.90, 56.32, 56.51, 56.65, 61.88, 62.66, 99.40, 105.81, 106.21, 106.42, 108.8, 115.25, 115.71, 117.20, 119.55, 123.84, 129.52, 130.63, 137.64, 139.07, 139.78, 146.87, 147.69, 151.18, 152.86, 153.58, 155.48, 159.29, 160.68, 175.52; [HRMS: M^+ Calcd. for $C_{30}H_{24}O_9$: 528.14202. Found: 528.1428].

Trimethoxycervinomycin A_1 secologue 27

To a solution of hexacyclic isocoumarin 26 (10 mg, 0.019 mmol) in CH_3OH (1.0 ml) was added 2-aminoethanol (10 mg, 0.016 mmol) in CH_3OH and the mixture stirred at room temp. for 36h. Usual work-up with CH_2Cl_2 afforded a product which could not be characterized. However, brief exposure of this product to borontrifluoride-etherate in CH_2Cl_2 at 0°C afforded 27 (7 mg, 70%) m.p. 300°C; IR (KBr): 3350, 1650, 1620, 1600, 1580, 1480, 1430, 1300, 1280, 1200, 1050, 730 cm^{-1}; ^1H NMR: δ 2.42 (3H, s), 3.32 (3H, s), 4.0 (3H, s), 4.06 (3H, s), 4.14 (3H, s), 4.20 (3H, s), 4.0-4.5 (4H, m), 6.72 (1H, s), 7.0 (1H, s), 7.10 (1H, s), 7.66 (1H, d, J=9Hz), 7.7 (1H, s), 8.16 (1H, d, J=9Hz) [LRMS: m/z = 571 (M^+, 100%)].

3-Acetylmethyl-1,7,10,11,14-pentamethoxynaphtho[1,2-b]xanthone-2-carboxylic acid methyl ester 28

The ketoacid 24 (R=H) (0.1g, 0.18 mmol) was taken in CH_2Cl_2 (5 ml) and ethereal diazomethane was added for esterification. The solvent was removed and the residue was chromatographed over SiO_2-gel column using 2% $CH_3OH/CHCl_3$ as an eluent to furnish a mixture of (E,Z)-ketoester 24 (86 mg, 85%) which was irradiated in CH_2Cl_2 (200 ml) in the presence of catalytic I_2 for 10 min. Solvent was removed and the residue was chromatographed using 3:2:1 $CHCl_3$:ethyl acetate:hexane mixture as an eluent to give pentacyclic ketoester 28 (21 mg, 25%); m.p. 186°C; IR (KBr): 1720, 1650, 1610, 1580, 1480, 1460, 1430, 1280, 1110 cm^{-1}; ^1H NMR: 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), 7.0 (1H, s), 7.4 (1H, s), 7.62 (1H, d, J=9.0Hz), 7.66 (1H, s), 8.02 (1H, d, J=9.0Hz); ^{13}C NMR: δ 29.47, 47.94, 52.36, 56.24, 56.42, 60.77, 62.12, 62.30, 99.30, 106.01, 114.54, 115.83, 117.83, 119.71, 121.30, 124.48, 127.54, 130.18, 130.01, 131.54, 135.01, 137.83, 146.77, 147.71, 151.01, 155.31, 156.12, 157.07, 168.83, 175.36, 205.25; [LRMS: m/z = 560 (M^+, 20%), 529 (100%)].

(E,Z)-2,3,10,10a-Tetrahydro-6-methoxy-10a-methyl-8-[(1,4,6,7-tetramethoxyxanthon-3-yl)ethen-2-yl]oxazolo[3,2-b]isoquinolin-5-one 6

To a stirred solution of ketoester 24 (10 mg, 0.018 mmol) in CH_2Cl_2 (0.5 ml) was added 2-aminoethanol (10 mg, 0.16 mmol) in CH_3OH (0.2 ml) and the resulting mixture was stirred for 80h at room temp. The solvent was removed and the residue was chromatographed over SiO_2-gel using 2% CH_3OH/CH_3Cl to yield oxazolo-isoquinolinone derivative 6 (6.5 mg, 63%) as

an (E,Z)-mixture; IR (KBr): 1640, 1620, 1600, 1480, 1430, 1400, 1290, 1220, 1120 cm^{-1}; [LRMS: m/z = 573 (M^+, 80%), 558 (100%)].

Cervinomycin A_1-trimethylether 5

(a) By photolysis of 6: The above product 6 was irradiated in CH_2Cl_2 (10 ml) containing catalytic of amount of I_2 in a quartz tube using pyrex filter, for 3 min. Solvent was removed and the residue was chromatographed over SiO_2-gel using 2% $CH_3OH/CHCl_3$ to give 5 (2.2 mg, 30%); m.p. > 300°C; IR (KBr): 1675, 1640, 1620, 1605, 1580, 1510, 1470, 1450, 1420, 1400, 1275, 1200, 1030, 1000 cm^{-1}; ^1H NMR: δ (400 MHz) 1.4 (3H, s), 3.21 (1H, d, J=14.9Hz), 3.29 (1H, d, J=14.9Hz), 3.65 (1H, m), 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), 7.02 (1H, s), 7.35 (1H, s), 7.63 (1H, d, J=9Hz), 7.75 (1H, s), 8.08 (1H, d, J=9Hz); [LRMS: m/z = 571 (M^+, 25%), 540 (100%)].

(b) From the pentacyclic ketoester 28: To a solution of 28 (5 mg, 0.009 mmol) in CH_3OH (0.1 ml) was added 2-aminoethanol (7 mg, 0.11 mmol) in CH_3OH (0.1 ml). After stirring for 72 h at room temp., the solvent was removed and the residue was chromatographed over SiO_2-gel to give 5 (2 mg, 40%) identical with that in the reaction described above.

Cervinomycin A_2-monomethyl ether 2

A mixture of cervinomycin A_1 trimethyl ether 5 (3 mg, 0.0053 mmol) and Ag_2O (0.5 mg) in dioxan (1 ml) was sonicated in the presence of a tiny drop of aqueous nitric acid (6N). The mixture was diluted with water and extracted with CH_2Cl_2 (3 x 5 ml). Usual work-up and chromatography over SiO_2-gel using 1% $CH_3OH/CHCl_3$ gave an orange crystalline compound identified as cervinomycin A_2 monomethyl ether 2 (R=CH_3, 2 mg, 67%); Alternately, 5 (4.5 mg, 0.0078 mmol) was dissolved in CH_2Cl_2 (0.5 ml) and CH_3CN (1.0 ml) was added with stirring followed by aq.ceric ammonium nitrate solution (10%, 0.5 ml). The resulting mixture was stirred for 5 minutes and the usual work-up followed by chromatography over SiO_2-gel gave 2 (R=CH_3, 4.3 mg, 93%); m.p. > 300°C; IR (KBr): 1690, 1650, 1615, 1450, 1270 cm^{-1}; ^1H NMR: δ 1.43 (3H, s), 3.27 (2H, d), 3.67 (1H, m), 4.01 (3H, s), 4.04 (3H, s), 4.21 (3H, s), 4.15-4.3 (3H, m), 7.16 (1H, s), 7.46 (1H, s), 7.66 (1H, s), 7.93 (1H, d, J=8.5Hz), 8.19 (1H, d, J=8.5Hz). The spectral data exactly matched those reported in the literature.

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