Total Synthesis of (±)-Mycelianamide

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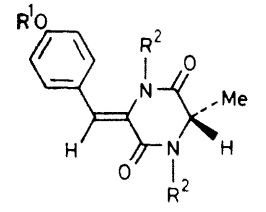
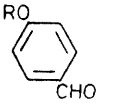
Summary The first total synthesis of the antibiotic (±)-mycelianamide has been achieved using *p*-geranyloxybenzaldehyde and ethyl nitroacetate as starting materials

THE antibiotic mycelianamide (**1**)[1,2] is a structurally unique member of the large group of biologically active diketopiperazines,[3] it is indeed the only known example of a cyclic arylidene bishydroxamic acid The structural assignment of mycelianamide is based upon a variety of degradative and spectroscopic evidence,[4] and is further supported by a synthesis of (±)-dideoxymycelianamide (**2**) [5] The only recorded attempts to synthesize mycelianamide itself were unsuccessful, owing to difficulties in producing the highly sensitive unsaturated bishydroxamic acid system from a variety of precursors [6] We now report refinements of the earlier synthetic approach which have led to the first total synthesis of (±)-mycelianamide

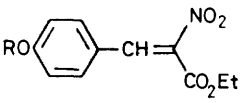
Alkylation of *p*-hydroxybenzaldehyde with geranyl bromide[7] and potassium carbonate in acetone gave *p*-geranyloxybenzaldehyde (**3**) in 79% yield Condensation of (**3**) with ethyl nitroacetate[8] (acetic acid, β-alanine catalyst) afforded a mixture of *E*- and *Z*-isomers of the α-nitrocinnamic ester (**4**) in 73% yield The olefinic bond of (**4**) was blocked by the Michael addition of benzeneselenol (pyridine catalyst), and the resulting adduct (**5**) was reduced directly by aluminium amalgam in moist ethyl acetate to give (50% yield from **4**) a 3:1 mixture of the *erythro*- and *threo*-isomers of the hydroxyamino ester (**6**)



(1) R^1 = geranyl, R^2 = OH

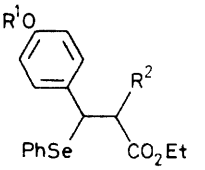


(3) R = geranyl



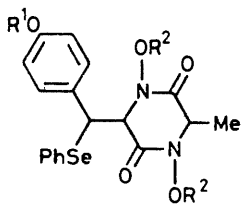
(2) R^1 = geranyl, R^2 = H

(4) R = geranyl



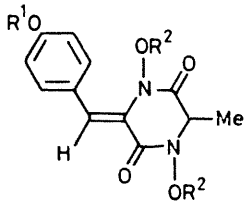
(5) R^1 = geranyl, R^2 = NO_2
(6) R^1 = geranyl, R^2 = NHOH
(7) R^1 = geranyl, R^2 = NOHCOCHBrMe

Acylation of (**6**) with α-bromopropionyl chloride in the presence of di-isopropylethylamine produced a mixture of the four possible diastereomers of (**7**), which was separable by medium-pressure chromatography (benzene–ethyl acetate on silica) [9]

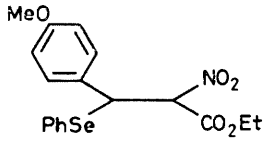


(8) R^1 = geranyl, R^2 = H

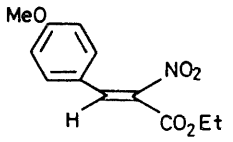
(9) R^1 = geranyl, R^2 = $SiMe_2Bu^t$



(10) R^1 = geranyl, R^2 = $SiMe_2Bu^t$



(11)



(12)

The major *erythro*-isomer of (**7**)[10] (38% yield) gave the cyclic bishydroxamic acid (**8**) (35%) on treatment with excess of free hydroxylamine in methanol. All attempts to convert (**8**) directly to mycelianamide by direct oxidative elmination of the phenylselenyl group failed. However, conversion of (**8**) into the corresponding bis-t-butyldimethylsilyl ether (**9**) (62% by t-butyldimethylsilyl chloride[11] and imidazole in dimethylformamide), followed by oxidation with *m*-chloroperbenzoic acid in tetrahydrofuran containing furan yielded, after 40 min at room temperature, the elimination product (**10**) (76%). Desilylation of (**10**) by aqueous hydrogen fluoride[12] in ethanol gave (±)-mycelianamide (**1**), 58%), m.p. 143—146 °C (decomp.). This material was identical spectroscopically (i.r., u.v., n.m.r., m.s.) with naturally derived mycelianamide.

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[9] Satisfactory i.r., n.m.r., and mass spectral data were obtained for each new compound isolated.

[10] The *erythro*- and *threo*-isomers of (**5**), (**6**), and (**7**) are readily distinguishable by n.m.r. spectroscopy, since in each case the CH_3 of the ethoxycarbonyl group of the *threo*-isomer is shielded (by the *p*-geranyloxyphenyl group) relative to the same group of the *erythro*-isomer. This generalization was supported by a model study in which the crystalline *erythro*-isomer of (**11**) gave exclusively the crystalline (*Z*)-ester (**12**) on oxidative deselenation with *m*-chloroperbenzoic acid. Details of this model study will be reported in our full paper.

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