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## Total Synthesis of $(\pm)$ -Mycelianamide

By NOBORU SHINMON and MICHAEL P CAVA\*

(Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104)

and Roger F C Brown

(Department of Chemistry, Monash University, Clayton, Victoria, Australia 3168)

Summary The first total synthesis of the antibiotic  $(\pm)$ -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,<sup>3</sup> 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,<sup>4</sup> and is further supported by a synthesis of  $(\pm)$ -dideoxymycelianamide (2) <sup>5</sup> 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 <sup>6</sup> We now report refinements of the earlier synthetic approach which have led to the first total synthesis of  $(\pm)$ -mycelianamide

Alkylation of p-hydroxybenzaldehyde with geranyl bromide<sup>7</sup> and potassium carbonate in acetone gave pgeranyloxybenzaldehyde (3) in 79% yield Condensation of (3) with ethyl nitroacetate<sup>8</sup> (acetic acid,  $\beta$ -alanine catalyst) afforded a mixture of E- and Z-isomers of the *a*-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)



Acylation of (6) with  $\alpha$ -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)<sup>9</sup>



(10) R<sup>1</sup>= geranyl , R<sup>2</sup>=SiMe<sub>2</sub>Bu<sup>t</sup> (8)  $R^{1}$ = geranyl,  $R^{2}$ =H (9) R<sup>1</sup>=geranyl, R<sup>2</sup>=SiMe<sub>2</sub>Bu<sup>t</sup>



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<sup>11</sup> 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<sup>12</sup> in ethanol gave  $(\pm)$ -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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Satisfactory i.r., n.m.r., and mass spectral data were obtained for each new compound isolated.

<sup>10</sup> The *erythro*- and *threo*-isomers of (5), (6), and (7) are readily distinguishable by n.m.r. spectroscopy, since in each case the CH<sub>3</sub> 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. <sup>11</sup> E. J. Corey and A. Venkateswarlu, J. Am. Chem. Soc., 1972, 94, 6190.

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