Biosynthesis of Austin, A Polyketide–Terpenoid Metabolite of *Aspergillus ustus*

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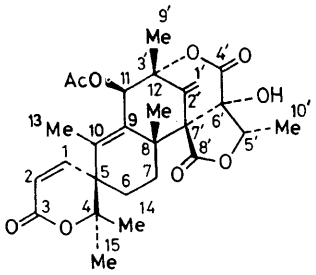
Summary Incorporations of [1-^{13}C]-, [2-^{13}C]-, [1,2-$^{13}C_2$]-acetates and [*Me*-^{13}C]methionine into austin, a metabolite of *Aspergillus ustus*, indicate its formation by a mixed polyketide–terpenoid biosynthetic pathway.

WE have recently carried out studies on andibenin[1] and anditomin,[2] complex C_{25} metabolites of *Aspergillus varie-color* which indicated their formation by a novel and elaborate extension of the triprenylphenol biosynthetic



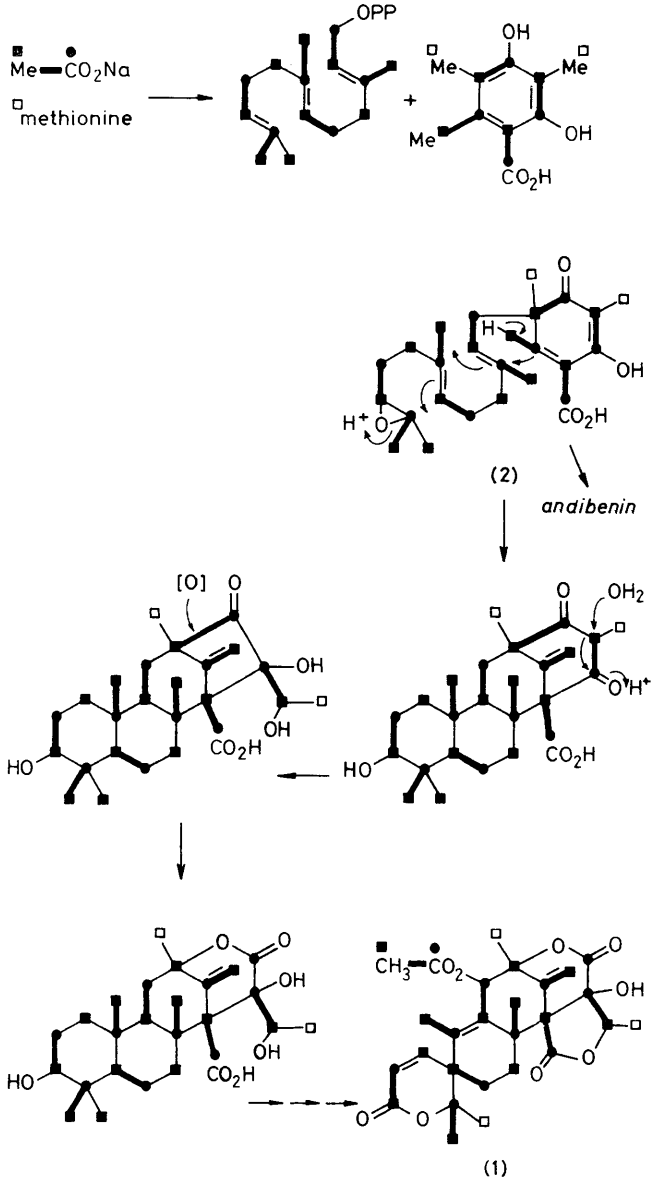
(1)

pathway,[3] in which a bis-*C*-methylated tetraketide-derived phenolic precursor is alkylated by farnesyl pyrophosphate to give the intermediate (**2**), Scheme, followed by further extensive modifications. We now report ^{13}C-labelling studies which indicate that the mycotoxin austin (**1**), a metabolite of *Aspergillus ustus* for which a sesterterpenoid origin has been proposed,[4] is also formed *via* (**2**) by a further variation of this pathway.

TABLE. ^{13}C-Chemical shifts (δ, relative to Me_4Si), coupling constants (Hz) from [1,2-$^{13}C_2$]acetate, and enrichments from [1-^{13}C]acetate (●), [2-^{13}C]acetate (*), and [*Me*-^{13}C]methionine (□) observed in austin.

Carbon	δ/p.p.m.	^1J(^{13}C–^{13}C)	Enrichment
1	146·5	—	*
2	120·2	66	●
3	163·6	67	*
4	85·5	42	●
5	46·6	34	*
6	27·0	34	●
7	26·5	—	*
8	42·1	34	●
9	132·6	46	*
10	143·8	43	●
11	74·7	47	●
12	23·5	35	*
13	15·4	44	*
14	22·4	42	*
15	25·9	—	*
1′	118·0	76	*
2′	137·5	76	●
3′	84·1	—	*
4′	170·1	—	●
5′	78·7	34	*
6′	80·6	34	●
7′	62·8	54	*
8′	170·8	54	●
9′	20·2	—	□
10′	11·3	—	□
CH_3CO	168·4	60	●
CH_3CO	20·6	61	*

After considerable experimentation, conditions were obtained which gave much improved yields (*ca.* 100 mg l^{-1}) of austin and satisfactory incorporation of acetate. The ^{13}C n.m.r. spectrum of austin was unambiguously assigned from chemical shift considerations, multiplicities in s.f.o.r.d. spectra, ^{1}H and ^{13}C chemical shift correlations, and analysis of long range couplings in fully ^{1}H-coupled ^{13}C spectra by



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extensive low power selective decoupling experiments. These studies gave the assignments listed in the Table. Incorporation of [1-^{13}C]-, [2-^{13}C]-, and [1,2-$^{13}C_2$]-acetate, and [*Me*-^{13}C]methionine gave the enrichments and ^{13}C–^{13}C couplings summarised in the Table. The resultant labelling pattern in austin is entirely consistent with the pathway shown in the Scheme in which formation of the key intermediate (**2**) is followed by formation of the C(8)–C(7′) bond, ring contraction, and oxidative cleavage of the phenolic ring, and elaboration of the farnesyl moiety to the terpenoid spiro-lactone ring system, although the sequence in which these processes occur is uncertain. The required degree of modification of the precursor tetraketide is quite exceptional.

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