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BIOSYNTHESIS OF HIGHLY MODIFIED MEROTERPENOIDS IN ASPERGILLUS VARIECOLOR. INCORPORATION OF ^{13}C-LABELLED ACETATES AND METHIONINE INTO ANDITOMIN AND ANDILESIN C

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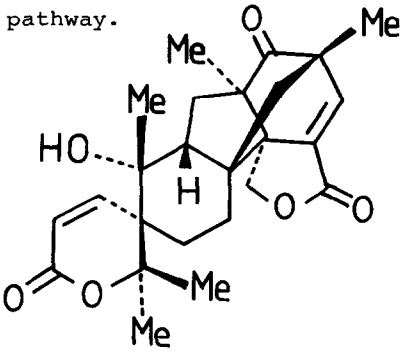
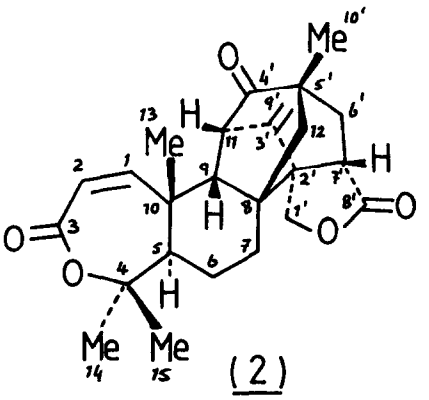
Summary: Incorporations of [1-^{13}C]-, [2-^{13}C]-, [1,2-$^{13}C_2$]-acetates and [^{13}C]-methionine into anditomin, a metabolite of Aspergillus variecolor, indicate its formation by a mixed polyketide-terpenoid biosynthetic pathway similar to that elucidated for andibenin; observations are made on the possible biosynthetic relationship of the A. variecolor metabolites with austin and terretonin, mycotoxins recently isolated from A. ustus and A. terreus respectively.

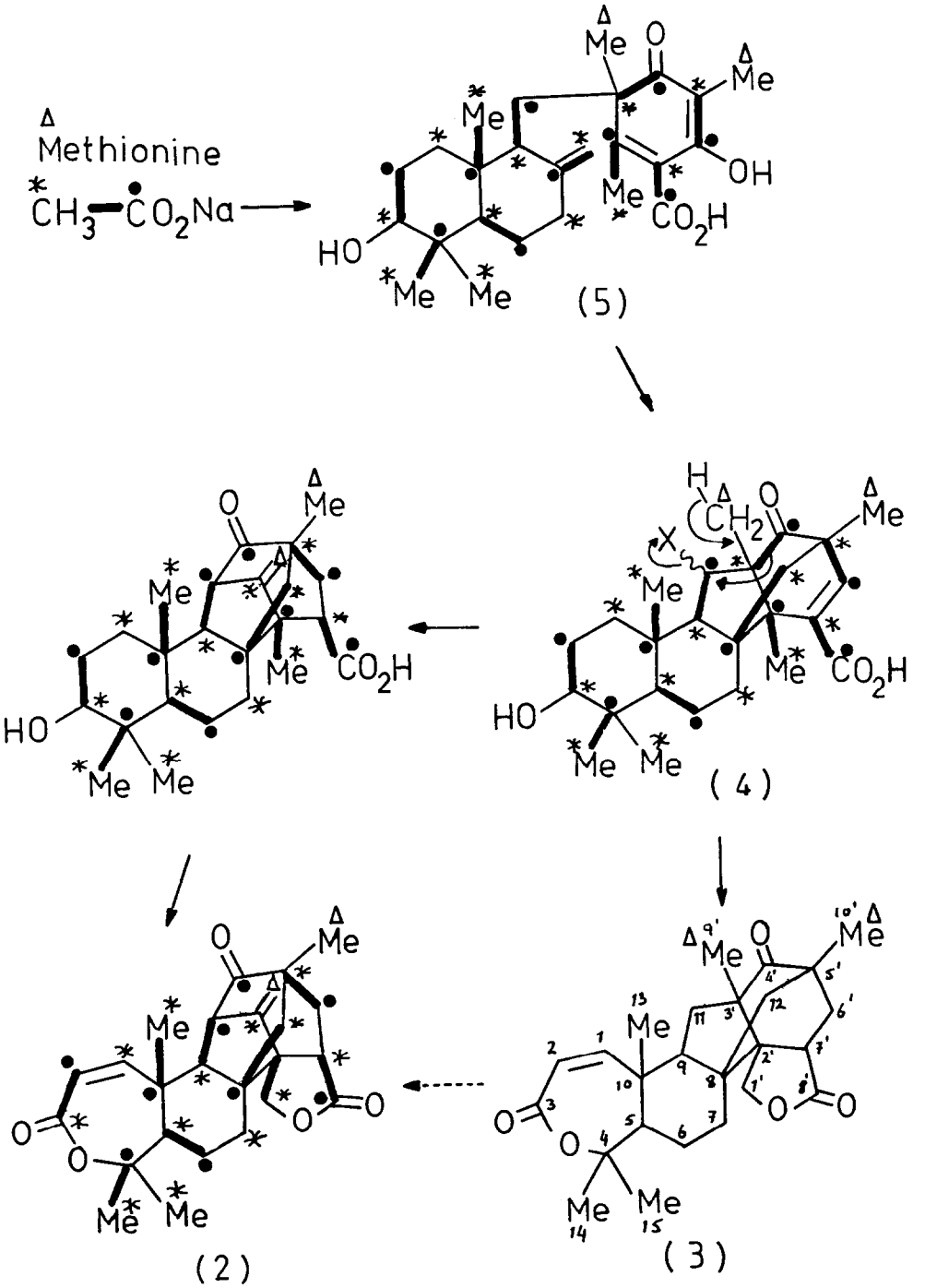
We recently reported incorporation studies[1] on andibenin (1) a complex C_{25} metabolite of Aspergillus variecolor for which a sesterterpenoid origin had been proposed.[2] These studies indicated biosynthesis of andibenin via alkylation of a bis-C-methylated tetraketide-derived phenolic precursor by farnesyl pyrophosphate, followed by drimane-type cyclisation of the farnesyl moiety, intramolecular 4 + 2 cycloaddition, and oxidative modifications and rearrangement. This pathway represented a unique and elaborate variation of the triprenylphenol pathway which is not uncommon among fungi and marine organisms. We now wish to report studies on anditomin (2) and andilesin (3), co-metabolites in A. variecolor (CMI 60316),[3] which parallel those on andibenin and which indicate a further elaboration of this pathway.



(1)



(2)



Scheme

The ^{13}C nmr spectra of anditomin and andilesin C have been assigned from standard chemical shift date, multiplicities in s.f.o.r.d. spectra, ^{1}H-^{13}C decoupling experiments and ^{13}C-^{13}C coupling data and are summarised in the table. Incorporations of [^{13}C] methionine, [1-^{13}C]-, [2-^{13}C]-, and (1,2-^{13}C] acetates into anditomin (2) by cultures of A. variecolor resulted in the enrichments and ^{13}C-^{13}C couplings summarised in the table. In the case of andilesin C (3), low yields prevented determination of the [^{13}C] acetate enrichments but the efficient incorporation of methionine allowed the diagnostic enrichments of the 9' and 10' methyls to be ascertained. The resulting labelling pattern for anditomin is shown in the scheme and the important features are the lack of coupling between C-3' and C-4' indicating cleavage of the original polyketide-derived carbocyclic ring, and the derivation of the olefinic methylene carbon (C-9') from the C_1-pool. These results indicate the pathway shown in the scheme which proposes that anditomin is formed by a novel rearrangement of the andilesin skeleton or an immediate precursor. The actual timing and mechanism of the rearrangement relative to the other necessary modifications of the proposed intermediate (4) remain to be elucidated, and this together with other aspects of the mechanism of formation and biosynthetic inter-relationships among the andibenins and andilesins[4] are being investigated. The recent isolation of the astellolides,[5] drimane-type sesquiterpenoids from a mutant of the andibenin producing strain which appears to be impaired in polyketide synthesis; and stellatin,[5] a bis-C-methylated tetraketide from A. variecolor provide further indirect support for this biosynthetic pathway. The pathway may not be unique to A. variecolor as it is possible to account for the formation of both austin,[7] and terretonin,[8] mycotoxins isolated from A. ustus and A. terreus respectively for which sesterterpenoid and triterpenoid origins have been proposed, from the common intermediate (5). Studies to test whether these structurally diverse metabolites are indeed formed by variations of a common pathway are in progress.

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Table ^{13}C-Chemical Shifts (δ, relative to Me_4Si) of anditomin (2) and andilesin C (3); coupling constants (Hz) of [1,2-$^{13}C_2$] acetate-enriched (2) and enrichments observed in [1-^{13}C]acetate (•), [2-^{13}C]-acetate (*) enriched (2), and [Me-^{13}C] methionine (Δ) enriched (2) and (3).

carbon	δ/p.p.m. (2)	$^1J(^{13}C-^{13}C)$	δ/p.p.m. (3)
1	147.4 *[a]	-	149.5
2	120.1 •[a]	68	119.4
3	165.9 *	68	166.2
4	83.6 •	37	83.5
5	44.5 *	34	42.2
6	21.0 •	34	22.8
7	25.7 *	-	24.7
8	47.7 •	33	45.3
9	61.5 *	29	56.4
10	44.4 •	32	43.8
11	64.1 •	29	38.7
12	49.8 *	33	52.7
13	25.9 *	32	22.4
14	30.6 *	-	30.2
15	23.2 *	38	23.5
1'	75.5 *	35	69.2
2'	42.6 •	35	43.1
3'	148.0 *	-	56.8
4'	207.9 •	-	216.5
5'	54.1 *	34	55.0
6'	30.6 •	34	32.3
7'	43.2 *	55	35.5
8'	173.8 •	56	176.2
9'	111.4 Δ[b]	-	19.5 Δ[b]
10'	23.7 Δ	-	16.8 Δ

[a] enrichment ca 1 atom % [b] enrichment ca 10 atom %

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