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Asymmetric synthesis of passifloricin A: a correction in structure

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Abstract—The structure reported in the literature for the pharmacologically active, natural lactone passifloricin A (δ-lactone of 2*Z*,5*R***S**,7*R**,9*S**,11*S**-tetrahydroxyhexacos-2-enoic acid) is incorrect not only as regards stereochemical issues, but also in the placement of one of the hydroxyl groups of the side chain. By means of an unambiguous synthesis, passifloricin A is shown to be the δ-lactone of 2*Z*,5*R*,7*S*,9*S*,12*S*-tetrahydroxyhexacos-2-enoic acid. All of the stereogenic centres were created with the aid of Brown's asymmetric allylation methodology. The lactone ring was made via ring-closing metathesis.

Lactone rings are a structural feature of many natural products.[1,2] Many naturally occurring lactones, particularly those that are Michael acceptors (α,β-unsaturated),[3] display pharmacologically interesting properties, e.g. some exhibit antitumour activity while others are tumour-promoting. Two years ago, one such lactone, the polyketide-type α-pyrone passifloricin A, was isolated with other closely related lactones from the resin of *Passiflora foetida* var. *hispida*, a species from the family Passifloraceae that grows in tropical zones of America. On the basis of purely spectroscopic findings, the structure of passifloricin A was originally proposed to be **1** (Fig. 1), although not all of the stereogenic centres were assigned relative configurations with the same amount of confidence. Indeed, the configuration at C-5 relative to the other stereocentres[4] could not be established on the basis of the available data; therefore, two epimeric structures were possible for the natural lactone. The absolute configuration was thus left undetermined.

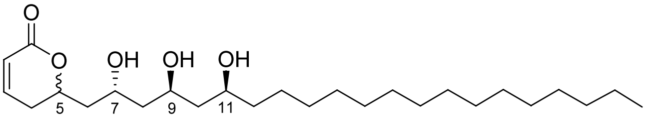

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Figure 1. Structures initially proposed for passifloricin A (configuration at C-5 undetermined).

Since this research falls within our general interest in the stereoselective synthesis of bioactive natural lactones,[5] and with the uncertainty in the proposed structure in mind, we set out to determine the structure of passifloricin A, including its absolute configuration, by means of total synthesis. We have thus recently published the stereoselective synthesis of the two epimers at C-5 represented by structure **1**.[6] As neither of these turned out to be identical with the natural product,[7] we synthesized two additional stereoisomers, but again, both were found to be distinctly different from the natural lactone.[8]

It was at this point that we started having serious doubts about the validity of some of the data presented in the original paper.[4] One of these was the assertion that two of the hydroxyl groups were arranged in a *syn*-1,3 fashion. This conclusion, which seems well-founded, was based on NOE measurements and the ^{13}C NMR data of an acetonide formed in the reaction of lactone **1** with acetone and an acid catalyst. However, the same reaction was said to generate a second compound which, in the opinion of the authors, was the acetonide of an *anti*-1,3-diol. This conclusion was based on the observation of an NOE between one acetonide methyl and only one proton in the δ 3–5 range, thought to be H-7. Unfortunately, the isolated amount of this second compound was too small to allow for the measurement of a ^{13}C NMR spectrum. Logically, however, if these data were correct, the only possible structures for the natural compound or for its enantiomer were the two structures **1** epimeric at C-5. As this was

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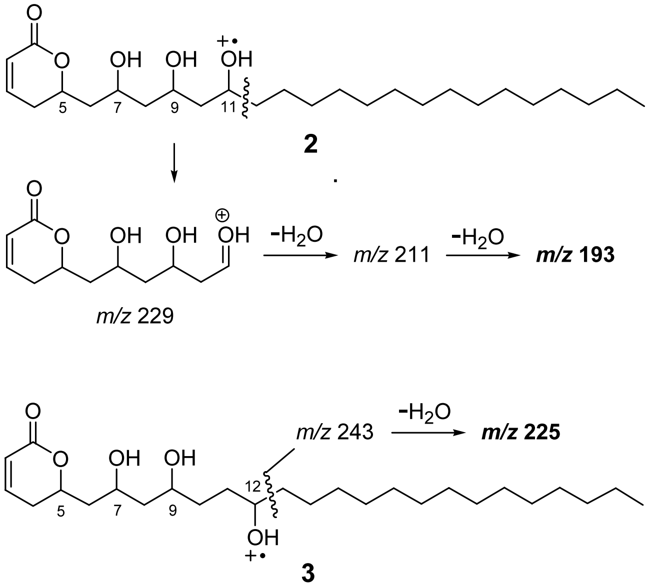
obviously not the case, part of the presented data were necessarily erroneous.

One point that caught our attention was the NMR data. When we synthesized the four aforementioned stereoisomers of general structure **2** (Scheme 1), we found that their ^{1}H and ^{13}C NMR spectra were very similar. Spin decoupling was not overly helpful in assigning the proton signals due to strong overlapping. As a consequence, many ^{13}C NMR signals could not be individually assigned, even when using combined HMQC/HMBC measurements at 500 MHz. However, one feature of the ^{13}C NMR data was noteworthy, namely that all four spectra showed *three* signals in the range 40–45 ppm, whereas passifloricin A showed only *two*. According to our heteronuclear 2D measurements, these were the methylene signals of the CH(OR)**CH$_2$**CH(OR) fragments (C-6/C-8/C-10 in **1**). This finding suggested that the natural lactone had only two moieties of this class. Consequently, one of the hydroxyl groups was misplaced. This finding alone, however, opened too many structural possibilities.

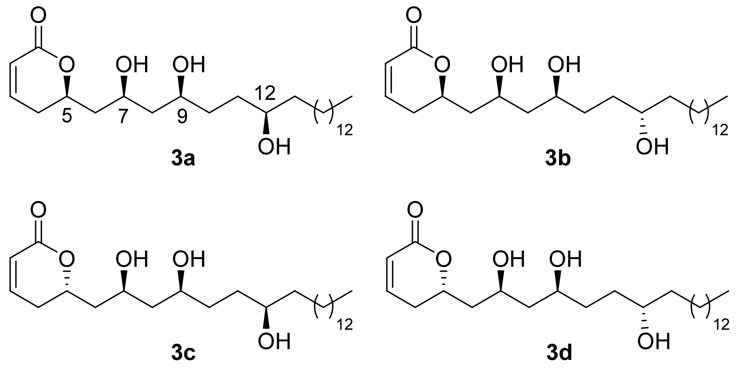


Scheme 1. Ion fragmentations in the mass spectra of structures **2** and **3**.

We thus turned our attention to another spectral feature, namely the prominent peak at *m*/*z* 225 in the mass spectrum of passifloricin A. While the four stereoisomers of **2** synthesized by us displayed very similar mass spectra, none of them showed a peak at *m*/*z* 225 (10% relative intensity at most). Conversely, the intense peak appearing at *m*/*z* 193 (80–100%) in all four spectra was absent in the mass spectrum of passifloricin A. This latter peak was mechanistically explained, as shown in Scheme 1, by invoking the known tendency of alcohol parent peaks to undergo α-cleavage with charge retention at the oxygen-bearing fragment (protonated carbonyl ion).[9] The resulting ion was then seen to lose two successive water molecules to yield *m*/*z* 193 (the intermediate peaks at *m*/*z* 229 and *m*/*z* 211 were also visible although weak). In order to explain the absence of the peak at *m*/*z* 193 and the presence of a strong peak at *m*/*z* 225 in the mass spectrum of passifloricin A on the one hand and to account for the aforementioned NMR features on the other, we reasoned that the hydroxyl at C-11 in structure **2** should be shifted to C-12 as in **3** (Scheme 1). Assuming that this alternative structure was a reasonable possibility for passifloricin A, we decided to undertake its synthesis.

We started out with the assumption that even if the reported formation of the acetonide of an *anti*-1,3-diol from passifloricin A was no longer tenable,[4] the formation of the acetonide of a *syn*-1,3-diol was still true. The 1,3-diol moiety of structure **3** was thus fixed in a *syn* relationship and the other stereogenic centres were allowed to vary. In order to reduce the amount of synthetic work, we aimed to synthesize only one of the two possible configurations for the 1,3-diol moiety; thus, we would end up with either natural passifloricin A or its unnatural enantiomer. This reasoning led us to propose the four stereoisomeric structures **3a**–**d** as our synthetic targets (Scheme 2).

The new retrosynthetic concept deviates only slightly from that proposed in our previous communication[6] and relies once again upon Brown's asymmetric allylations to create new C–C bonds and stereogenic centres.[10] The only difference is that, due to the one-carbon shift of the first hydroxyl function, the initial asymmetric allylation was followed by hydroboration–oxidation of the olefinic bond, instead of oxida-

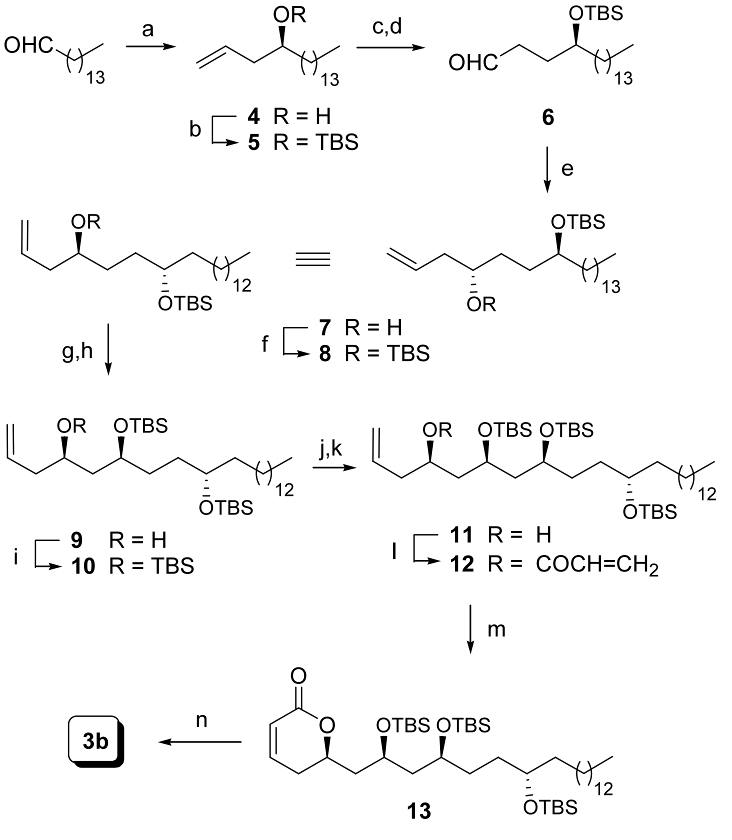


Scheme 2. The possible stereoisomeric structures of passifloricin A or its enantiomer.

tive cleavage.[6] The unsaturated lactone ring was formed, as previously, via ring-closing metathesis (RCM).[11] For the sake of brevity, only the synthesis of stereoisomer **3b**, which proved identical to passifloricin A, is described hereafter.[12]

n-Pentadecanal[13] was reacted with B-allyl di*iso*pinocampheylborane (allylBIpc$_2$), prepared from allylmagnesium bromide and (+)-di*iso*pinocampheylboron chloride ((+)-DIP-Cl).[10] This gave homoallyl alcohol **4** as a 96:4 enantiomeric mixture (Scheme 3), as judged from NMR analysis of the Mosher ester. Protection of the hydroxyl group as the *t*-butyldimethylsilyl derivative was followed by hydroboration of the olefinic bond to yield a primary alcohol. Swern oxidation of the latter gave γ-silyloxy aldehyde **6**, which was subjected to asymmetric allylation with the same reagent as above without further chromatographic purification. This gave homoallyl alcohol **7**, which was then silylated to **8**. Oxidative cleavage of the olefinic bond in the latter compound was followed by asymmetric allylation with the same reagent as above. This afforded the protected triol **9**, which was silylated to **10** and subjected once more to the same protocol to yield alcohol **11**, with the hydroxyl function suitably placed to build up the unsaturated lactone ring. Compound **11** was thus treated with acryloyl chloride to furnish the corresponding acrylate **12**. RCM with the standard Grubbs' ruthenium catalyst[11] gave the desired lactone **13**. Finally, acid-catalyzed cleavage of all the silyl protecting groups in **13** afforded lactone **3b** in a 92% yield. The NMR data of synthetic **3b** proved identical to those published for the natural product.[4,14,15] Furthermore, treatment of lactone **3b** with acetone and an acid catalyst gave only one acetonide, the NMR features of which were identical to those of the acetonide prepared from the natural product.[4]

In summary, we have performed a stereoselective, asymmetric synthesis of the natural lactone passifloricin A. This has led not only to a correction of the published structure and to the establishment of the absolute configuration, but also to the preparation of sizeable amounts of the compound for the evaluation of its



Scheme 3. Stereoselective synthesis of compound **3b** (passifloricin A). *Reagents and conditions*: (a) allylBIpc$_2$ [from (+)-DIP-Cl and allylmagnesium bromide], Et$_2$O, 1 h, −100°C (75%, 96:4 enantiomeric mixture). (b) TBSCl, DMF, imidazole, rt, 18 h, 80%. (c) 9-BBN, THF, rt, 20 h, then H$_2$O$_2$, NaOH, EtOH, 50°C, 1 h, 82%. (d) Swern oxidation. (e) AllylBIpc$_2$ [from (+)-DIP-Cl], Et$_2$O, −100°C (55% overall for the two steps, 94:6 diastereomeric mixture). (f) TBSOTf, 2,6-lutidine, rt, 1 h, CH$_2$Cl$_2$, 85%. (g) O$_3$, CH$_2$Cl$_2$, −78°C, then PPh$_3$, 3 h, rt. (h) AllylBIpc$_2$ [from (+)-DIP-Cl], Et$_2$O, 1 h, −100°C (after stereoisomer separation, 64% overall of compound **9**). (i) TBSOTf, 2,6-lutidine, rt, 1 h, CH$_2$Cl$_2$, 95%. (j) O$_3$, CH$_2$Cl$_2$, −78°C, then PPh$_3$, 3 h, rt. (k) AllylBIpc$_2$ [from (+)-DIP-Cl], Et$_2$O, 1 h, −100°C (95:5 diastereomeric mixture, then stereoisomer separation, 63% overall of compound **11**). (l) Acryloyl chloride, EtN*i*Pr$_2$, CH$_2$Cl$_2$, −78°C, 1.5 h, 81%. (m) 10% PhCH=RuCl$_2$(PCy$_3$)$_2$, CH$_2$Cl$_2$, Δ, 2.5 h, 86%. (n) PPTS, aq MeOH, 70°C, 18 h, 92% (Ipc, isopinocampheyl; TBS, *t*-butyldimethylsilyl; 9-BBN, 9-borabicyclo[3.3.1]nonane; PPTS, pyridinium *p*-toluenesulfonate).

biological properties.[12] Most likely, the structures of the other polyketide lactones isolated from *P. foetida* will also have to be revised.

Acknowledgements

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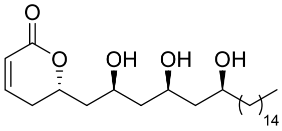
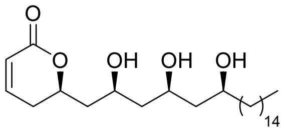
7. After our communication (Ref. 6) had appeared, a second report on the synthesis of the same two compounds was published: BouzBouz, S.; Cossy, J. *Tetrahedron Lett.* **2003**, *44*, 4471–4473. The retrosynthetic concept used by these authors is identical in its essence to our own, except for the use of chiral allyltitanium reagents instead of allylboranes.
8. These were the two following stereoisomers:





The second one is the enantiomer of a natural lactone isolated from *Eupatorium pilosum* (Herz, W.; Ramakrishnan, G. *Phytochemistry* **1978**, *17*, 1327–1332). The spectral properties of the synthetic compound were found to be identical with those published for the natural product. Their optical rotations showed obviously opposite signs (unpublished results).

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12. Details of the synthesis of compounds **3a**–**d** and evaluation of their cytotoxic properties will be reported in due course. This work is part of the projected Ph.D. thesis of J.G.-F.
13. Freshly prepared by PCC oxidation of *n*-pentadecanol.
14. We were able to compare our synthetic compound with an authentic sample of the natural compound. According to the NMR spectra of a mixture of natural passifloricin A and our synthetic compound **3b**, both compounds are identical. However, the reported numerical value of the optical rotation of passifloricin A is very different to that found by us (see Ref. 15). This may be due to the optical rotation having been measured in methanol (Ref. 4), in which passifloricin A has a low solubility. Indeed, we have observed that this gives rise to an inhomogeneous solution and thus to erratic values. We then measured the optical rotation in $CHCl_3$ solution, where the natural product is more soluble. The synthetic and the natural product were then found to have almost identical optical rotations.
15. Synthetic compound **3b**: white powder, mp 103–106°C (from EtOAc–MeOH), lit.[4] for passifloricin A, mp 97°C; $[\alpha]_D^{25} = +28.9$ (*c* 0.8; MeOH), lit.[4] for passifloricin A, $[\alpha]_D^{20} = +123.45$ (*c* 0.11; MeOH); $[\alpha]_D^{25} = +33.3$ (*c* 0.8; $CHCl_3$) for synthetic **3b**; $[\alpha]_D^{25} = +34.1$ (*c* 0.5; $CHCl_3$) for a sample of natural passifloricin A. The NMR spectra of synthetic **3b** are identical to those of the natural sample and to those of a mixture of natural and synthetic compound.