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On the Structure of Passifloricin A: Asymmetric Synthesis of the δ-Lactones of (2*Z*,5*S*,7*R*,9*S*,11*S*)- and (2*Z*,5*R*,7*R*,9*S*,11*S*)-Tetrahydroxyhexacos-2-enoic Acid

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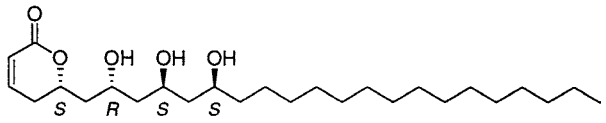
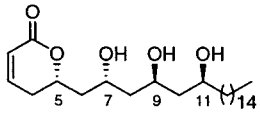
ABSTRACT



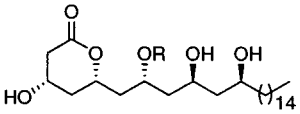
Published structure for passifloricin A

Stereoselective syntheses of the δ-lactone of (2*Z*,5*S*,7*R*,9*S*,11*S*)-tetrahydroxyhexacos-2-enoic acid, the structure reported for passifloricin A, and of its (5*R*)-epimer are described. The creation of all stereogenic centers relied upon Brown's asymmetric allylation methodology. The lactone ring was created via ring-closing metathesis. The NMR data of both synthetic products, however, were different from those of the natural product. The published structure of passifloricin A is thus erroneous and will require further synthetic work to be unambiguously assigned.

Lactone rings constitute a structural feature of many natural products.[1,2] Many naturally occurring lactones, particularly those that are Michael acceptors (α,β-unsaturated),[3] display pharmacological properties of interest, e.g., some exhibit antitumoral activity, while others are tumor promoting. One such lactone is the polyketide-type α-pyrone passifloricin A **1**, isolated two years ago, together with the closely related passifloricins B **2** and C **3**, from the resin of *Passiflora foetida* var. *hispida*, a species from the family Passifloraceae that grows in tropical zones of America. Their structures were elucidated on the basis of purely spectroscopic findings, but only the relative configuration of the stereogenic centers was given. Conjugated lactone **1** was found to be active in the *Artemia salina* test, whereas the unconjugated lactones **2** and **3** showed no activity.[4]



1



2 R = H **3** R = Ac

Within our recently initiated program on synthesis of bioactive lactones where ring-closing metathesis (RCM) reactions are used as one of the key steps,[5] we decided to undertake a stereoselective synthesis of **1** with the additional aim of establishing the absolute configuration of the natural

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(1) Negishi, E.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707−6738.
(2) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377−1395.
(3) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed.* **1985**, *24*, 94−110.
(4) Echeverri, F.; Arango, V.; Quiñones, W.; Torres, F.; Escobar, G.; Rosero, Y.; Archbold, R. *Phytochemistry* **2001**, *56*, 881−885.

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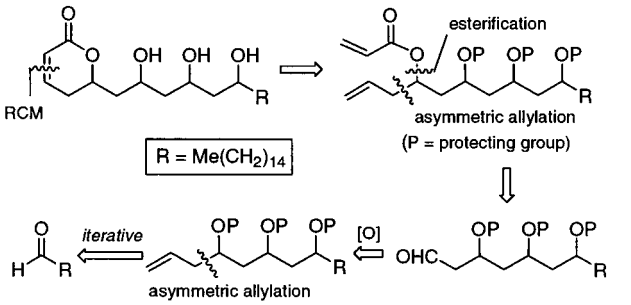
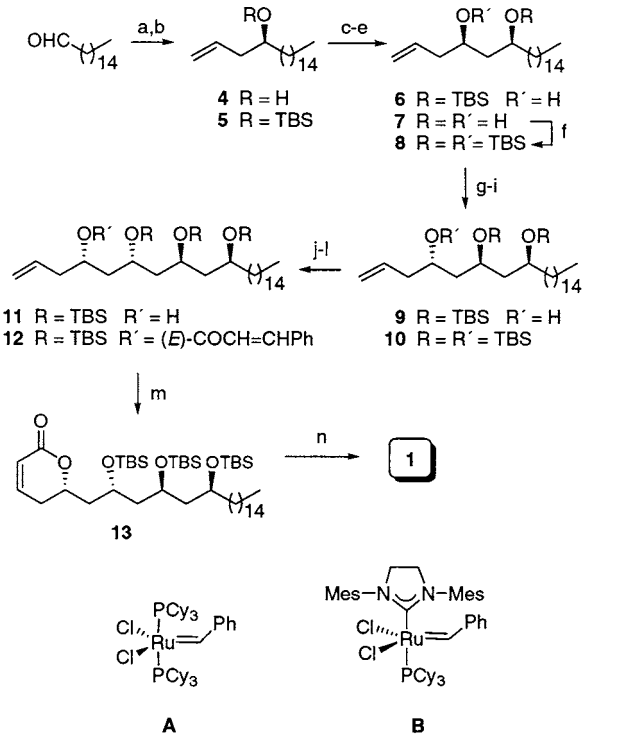
molecule. To start with, we selected the (5*S*,7*R*,9*S*,11*S*)-diastereoisomer, arbitrarily depicted for **1** in the original paper, as the target molecule. The 1,3-polyol segment of lactone **1** suggested several synthetic approaches.[6,7] Our retrosynthetic concept, depicted in Scheme 1, relied exclusively upon asymmetric allylations to create new C−C bonds. Starting with *n*-hexadecanal, an iterative three-step sequence (asymmetric allylation/hydroxyl protection/C=C oxidative cleavage) was conceived to create a new stereogenic carbon atom in each cycle. Acylation of the hydroxyl group generated in the last cycle, followed by ring-closing metathesis,[8] should finally afford the desired unsaturated lactone.

Scheme 1



In view of our favorable experiences with asymmetric allylations using Brown's chiral allylboranes,[5d,f] we selected this methodology for the present purposes.[9−11] Thus, *n*-hexadecanal[12] was allowed to react with B-allyl diisopinocampheylborane (allylBIpc$_2$), prepared from allylmagnesium bromide and (+)-DIP−Cl (diisopinocampheylboron chloride).[13] This gave homoallyl alcohol **4** as a 96:4 enantiomeric mixture (Scheme 2), as judged from NMR analysis of the Mosher ester. Protection of the hydroxyl group as the *tert*-butyldimethylsilyl derivative[14] was followed by ozonolysis of the olefinic bond to yield the intermediate β-silyloxy aldehyde, which without chromatographic purification was subjected to asymmetric allylation with the same reagent as above. This gave homoallyl alcohol **6**[15] with the desired syn relative configuration of the two oxygen functions.[16] Silylation to **8**[15] and oxidative cleavage of the olefinic bond was followed by asymmetric allylation of the intermediate β-silyloxy aldehyde. The allylating reagent was now

Scheme 2[a]



[a] Reagents and conditions: (a) allylBIpc$_2$ [from (+)-DIP−Cl and allylmagnesium bromide], Et$_2$O, 1 h, −100 °C (82%, 96:4 enantiomeric mixture). (b) TBSCl, DMF, imidazole, rt, 18 h, 93%. (c) O$_3$, CH$_2$Cl$_2$, −78 °C, then PPh$_3$, 3 h, rt. (d) AllylBIpc$_2$ [from (+)-DIP−Cl], Et$_2$O, −100 °C, (64% overall for the two steps, 93:7 diastereomeric mixture). (e) TBAF, THF, rt, 1.5 h, then chromatographic separation of the two diastereomers, 75% yield of pure **7**. (f) TBSOTf, 2,6-lutidine, rt, 1 h, CH$_2$Cl$_2$., 86%. (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 (82:18 diastereomeric mixture), then stereoisomer separation, 60% overall. (i) TBSOTf, 2,6-lutidine, rt, 1 h, CH$_2$Cl$_2$., 94%. (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 (91:9 diastereomeric mixture), then stereoisomer separation, 64% overall. (l) (*E*)-Cinnamoyl chloride, NEt$_3$, cat. DMAP, CH$_2$Cl$_2$, rt, 3 h, 76%. (m) 10% catalyst **B**, CH$_2$Cl$_2$, Δ, 3 h, 77%. (n) PPTS, aqueous MeOH, 70 °C, 18 h, 75% (TBS = *tert*-butyldimethylsilyl).

(5) (a) Carda, M.; Rodríguez, S.; Segovia, B.; Marco, J. A. *J. Org. Chem.* **2002**, *67*, 6560−6563. (b) Carda, M.; González, F.; Castillo, E.; Rodríguez, S.; Marco, J. A. *Eur. J. Org. Chem.* **2002**, 2649−2655. (c) Murga, J.; Falomir, E.; García-Fortanet, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2002**, *4*, 3447−3449. (d) Falomir, E.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2003**, *44*, 539−541. (e) Carda, M.; Rodríguez, S.; Castillo, E.; Bellido, A.; Díaz-Oltra, S.; Marco, J. A. *Tetrahedron* **2003**, *59*, 857−864. (f) Murga, J.; García-Fortanet, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2003**, *44*, 1737−1739.

(6) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635−645.

(7) For further, more recent methodologies toward 1,3-polyol segments, see, for example: (a) Palomo, C.; Aizpurua, J. M.; Urchegi, R.; García, J. M. *J. Org. Chem.* **1993**, *58*, 1646−1648. (b) Schneider, C.; Rehfeuter, M. *Chem. Eur. J.* **1999**, *5*, 2850−2858. (c) Trieselmann, T.; Hoffmann, R. W. *Org. Lett.* **2000**, *2*, 1209−1212. (d) Sarraf, S. T.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 3205−3208. (e) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 2777−2780. See also ref 11b.

(8) (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (b) Trnka, T.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29.

(9) Allylation under Keck and related conditions (ref 10) was unsuccessful here (extremely slow reaction). The use of the Duthaler−Hafner allylation reagent (ref 11) was discarded because of its very high price.

(10) (a) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467−8468. (b) Doucert, H.; Santelli, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4163−4169.

(11) (a) Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807−832. (b) Cossy, J.; BouzBouz, S.; Pradaux, F.; Willis, C.; Bellosta, V. *Synlett* **2002**, 1595−1606.

(12) Freshly prepared by PCC oxidation of *n*-hexadecanol.

(13) (a) Ramachandran, P. V.; Chen, G.-M.; Brown, H. C. *Tetrahedron Lett.* **1997**, 2417−2420. (b) For a recent review on asymmetric allylborations, see: Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23−35.

(14) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999; pp 127−141.

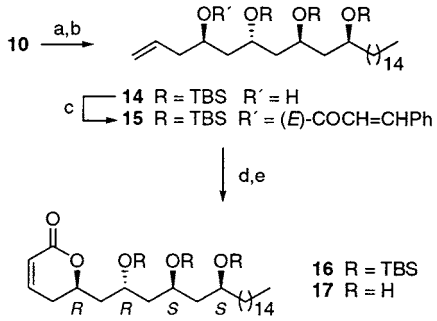
(15) Chomatographic separation of diastereomers (**6** + epimer) proved to be unfeasible. After desilylation, separation was possible and the pure diol **7** was then resilylated to **8**.

(16) This was shown by means of ^{13}C NMR and NOE measurements on the acetonide of diol **7**. See: Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9−17.

prepared from (−)-DIP−Cl and allylmagnesium bromide in order to have the desired (*S*)-configuration at the new stereogenic carbon. This afforded the protected triol **9**, which was silylated to **10** and subjected once more to the same protocol to yield alcohol **11**, where the hydroxyl function was suitably placed to build up the unsaturated lactone ring. To this end, **11** was treated with acryloyl chloride to furnish the corresponding acrylate. However, the yield was very low. In view of this, we made use of another recently proposed alternative. Alcohol **11** was treated with cinnamoyl chloride[17] to provide cinnamate **12** with good yield. Ester **12** proved to be unresponsive to RCM using the standard ruthenium complex **A** but gave the desired lactone **13** in the presence of the second-generation ruthenium catalyst **B**.[8] Finally, acid-catalyzed cleavage[18] of all silyl protecting groups in **13** gave lactone **1** in a very satisfactory 75% yield. Disappointingly, however, the NMR data of synthetic **1** proved to be distinctly different from those published for the natural product.[4,19] The optical rotation was also markedly different in value and opposite in sign.

In view of this unexpected result, we reexamined the available spectral data,[4] which served to elucidate the structure of passifloricin A. The authors based their stereochemical assignments on the formation of two monoacetonides through treatment of the natural product with acetone and an acid catalyst. In one of them, the dioxolane ring was located (HMBC experiments) between the C-9 and C-11 hydroxyl groups and found to be syn on the basis of ^{13}C NMR and NOE measurements. In the other acetonide, the dioxolane ring was located between the C-7 and C-9 hydroxyl groups and reported to be anti. However, the reasonings used to assign the (*S*)-configuration at C-5 were not well grounded, in our opinion. For this reason, we decided to synthesize the epimer of **1** having the (*R*)-configuration at this carbon atom. To this purpose, the β-oxygenated aldehyde resulting from the oxidative cleavage of compound **10** (Scheme 2) was reacted with an allylating reagent prepared from (+)-DIP−Cl and allylmagnesium bromide (Scheme 3). The resulting alcohol **14** was treated with cinnamoyl chloride to yield cinnamate **15**, which was then subjected to RCM using catalyst **B** to afford **16**. Cleavage of all protecting groups in **16** provided compound **17**, the epimer of **1** at C-5. Once again, however, the spectral data and the optical rotation of synthetic lactone **17** proved to be different from those of the natural product.[19]

Scheme 3[a]



[a] Reagents and conditions: (a) O_3, CH_2Cl_2, −78 °C, then PPh_3, 3 h, rt. (b) allylBIpc$_2$ [from (+)-DIP−Cl], Et_2O, 1 h, −100 °C (88:12 diastereomeric mixture), followed by chromatographic separation, 60% overall. (c) (*E*)-Cinnamoyl chloride, NEt_3, cat. DMAP, CH_2Cl_2, rt, 3 h, 77%. (d) 10% catalyst **B**, CH_2Cl_2, Δ, 3 h, 71%. (e) PPTS, aqueous MeOH, 70 °C, 18 h, 83%.

According to the data published by Echeverri and coworkers,[4] only the diastereoisomeric structures **1** and **17** should be possible for passifloricin A. We must therefore conclude that the data they presented are partly erroneous and that the structure they proposed for the natural lactone is incorrect as regards the configuration of some of the stereogenic centers. As a consequence, other stereoisomers of the δ-lactone of 5,7,9,11-tetrahydroxyhexacos-2-enoic acid (up to five)[20] will have to be prepared in order to establish the actual structure of passifloricin A. Work toward this goal is currently being performed in our laboratory and will be reported in due course.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **1** and **17** and tabulated IR and NMR data and optical rotation values for these compounds and for their peracetylated derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Ramachandran, P. V.; Chandra, J. S.; Reddy, M. V. R. *J. Org. Chem.* **2002**, *67*, 7547−7550.

(18) Basic desilylation reagent TBAF gives rise to lactone-opening reactions in this type of compound: Nakata, T.; Hata, N.; Oishi, T. *Heterocycles* **1990**, *30*, 333−334.

(19) Comparison with NMR spectra of the authentic sample showed clear differences, most particularly in the ^{13}C signals around 70 and 40 ppm.

(20) (5*S*,7*R*,9*R*,11*R*)-Stereoisomer, found in another plant source, is also different from passifloricin A. Its structure has been confirmed by stereoselective synthesis: Nakata, T.; Suenaga, T.; Nakashima, K.; Oishi, T. *Tetrahedron Lett.* **1989**, *30*, 6529−6532.