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Stereoselective Synthesis of the Antiprotozoal Lactone Passifloricin A and Seven Isomers Thereof

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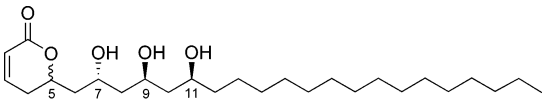
Received April 29, 2004

The conjugated δ-lactone passifloricin A, a natural product with antiprotozoal activity, and seven isomers thereof have been synthesized in enantiopure form. It has been shown in this way that the proposed structure for the natural compound was erroneous. The correct structure is now evidenced. Key steps of the syntheses were asymmetric Brown-type aldehyde allylations and ring-closing metatheses.

Introduction

Lactone rings are a structural feature of many natural products.[1] Many naturally occurring lactones, particularly those that are Michael acceptors (α,β-unsaturated),[1d] display a broad range of biological activities.[2,3] Three years ago, one such lactone, the polyketide-type α-pyrone passifloricin A, was isolated together with two 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.[4] The compound has been found to display interesting antiprotozoal properties.[5] On the basis of purely spectroscopic findings, the structure of passifloricin A was originally proposed to be either **1** or **2** (Figure 1), although not all of the stereogenic centers were assigned relative configurations with the same amount of confidence. Indeed, the configuration at C-5 relative to the other stereocenters could not be established on the basis of the available data and the absolute configuration was left undetermined.[4]



1 5αH
2 5βH

FIGURE 1. Structures initially proposed for passifloricin A.

Within our general interest in the stereoselective synthesis of bioactive natural lactones,[6] we set out to determine the structure of passifloricin A, including its absolute configuration, by means of total synthesis. Thus, we performed the stereoselective synthesis of structures **1** and **2**. Our synthetic concept (Scheme 1) relied on asymmetric allylations as the method to create the 1,3-polyol system[7] with its four stereocenters, whereas the lactone moiety was to be made by means of ring-closing metathesis (RCM).[8]

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(1) (a) Negishi, E.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707−6738. (b) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377−1395. (c) Carter, N. B.; Nadany, A. E.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2324−2342. (d) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94−110.

(2) The following types of pharmacological activity, among other examples, have been observed in lactones of various structures. (a) Vasodilating and antiarrhythmic effects: Leite, L.; Jansone, D.; Veveris, M.; Cirule, H.; Popelis, Y.; Melikyan, G.; Avetisyan, A.; Lukevics, E. *Eur. J. Med. Chem.* **1999**, *34*, 859−865. (b) Inhibition of the transcription factor NF-KB: Heinrich, M. *Phytother. Res.* **2000**, *14*, 479−488. Heinrich, M. *Curr. Top. Med. Chem.* **2003**, *3*, 141−154. (c) Eczematous allergic reactions: Reider, N.; Komericki, P.; Hausen, B. M.; Fritsch, P.; Aeerer, W.; Aberer, W. *Contact Dermatitis* **2001**, *45*, 269−272. Schempp, C. M.; Schopf, E.; Simon, J. C. *Hautarzt* **2002**, *53*, 93−97. (d) Inhibition of ribonucleotide reductase: Hakimelahi, G. H.; Moosavi-Movahedi, A. A.; Sambaiah, T.; Zhu, J. L.; Ethiraj, K. S.; Pasdar, M.; Hakimelahi, S. *Eur. J. Med. Chem.* **2002**, *37*, 207−217. (e) Antiinflammatory effects: Siedle, B.; Cisielski, S.; Murillo, R.; Loser, B.; Castro, V.; Klaas, C. A.; Hucke, O.; Labahn, A.; Melzig, M. F.; Merfort, I. *Bioorg. Med. Chem.* **2002**, *10*, 2855−2861. (f) Cytotoxicity: Lee, K. H.; Huang, B. R. *Eur. J. Med. Chem.* **2002**, *37*, 333−338. Hilmi, F.; Gertsch, J.; Bremner, P.; Valovic, S.; Heinrich, M.; Sticher, O.; Heilmann, J. *Bioorg. Med. Chem.* **2003**, *11*, 3659−3663. In many cases, it has been specifically demonstrated that the presence of a conjugated double bond is essential for the biological activity of the lactone because of its role as a Michael acceptor. See, for example: Buck, S. B.; Hardouin, C.; Ichikawa, S.; Soenen, D. R.; Gauss, C.-M.; Hwang, I.; Swingle, M. R.; Bonness, K. M.; Honkanen, R. E.; Boger, D. L. *J. Am. Chem. Soc.* **2003**, *125*, 15694−15695.

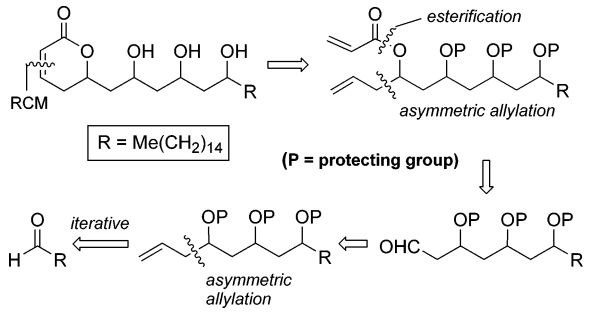
(3) For studies on the biological properties of lactones containing a 6-substituted 5,6-dihydropyran-2-one moiety, see, for example: (a) Stampwala, S. S.; Bunge, R. H.; Hurley, T. R.; Willmer, N. E.; Brankiewicz, A. J.; Steinman, C. E.; Smitka, T. A.; French, J. C. *J. Antibiot.* **1983**, *36*, 1601−1605. (b) Davis, R. M.; Richard, J. L. *Dev. Food Sci.* **1984**, *8*, 315−28. (c) Nagashima, H.; Nakamura, K.; Goto, T. *Biochem. Biophys. Res. Commun.* **2001**, *287*, 829−832. (d) Raoelison, G. E.; Terreaux, C.; Queiroz, E. F.; Zsila, F.; Simonyi, M.; Antus, S.; Randriantsoa, A.; Hostettmann, K. *Helv. Chim. Acta* **2001**, *84*, 3470−3476. (e) Kalesse, M.; Christmann, M. *Synthesis* **2002**, 981−1003. (f) Lewy, D. S.; Gauss, C.-M.; Soenen, D. R.; Boger, D. L. *Curr. Med. Chem.* **2002**, *9*, 2005−2032. (g) Larsen, A. K.; Escargueil, A. E.; Skladanowski, A. *Pharmacol. Ther.* **2003**, *99*, 167−181. (h) Richetti, A.; Cavallaro, A.; Ainis, T.; Fimiani, V. *Immunopharmacol. Immunotoxicol.* **2003**, *25*, 441−449.

(4) Echeverri, F.; Arango, V.; Quiñones, W.; Torres, F.; Escobar, G.; Rosero, Y.; Archbold, R. *Phytochemistry* **2001**, *56*, 881−885.

(5) Passifloricin A has been found to be active against some *Plasmodium* and *Leishmania* spp. (Echeverri, F. Personal communication).

10.1021/jo049275d CCC: $27.50
Published on Web 09/22/2004

SCHEME 1. Retrosynthetic Plan for Compounds 1 and 2



Results and Discussion

The synthesis of **1** and **2** is shown in Scheme 2 (experimental details in Supporting Information).[9] Asymmetric allylations were performed with Brown's chiral allylboranes.[10−13] Thus, *n*-hexadecanal[14] was allowed to react with the B-allyl diisopinocampheylborane (allyl-$BIpc_2$) prepared from allylmagnesium bromide and (+)-DIP−Cl (diisopinocampheylboron chloride).[10] This gave homoallyl alcohol **5** with a 96:4 enantiomeric ratio (er, Scheme 2), as judged from NMR analysis of the Mosher ester. Protection of the hydroxyl group as the *t*-butyldimethylsilyl (TBS) derivative[15] 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 **7**[16] (93:7 diastereomeric ratio, dr) with the desired syn relative configuration of the two oxygen functions.[17] Silylation to **9**[16] and oxidative cleavage of the olefinic bond was followed by asymmetric allylation of the intermediate *β*-silyloxy aldehyde. The allylating reagent was now 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 **10**, which was silylated to **11** and subjected once more to the same protocol to yield alcohol **12**, where the hydroxyl function was suitably placed to build up the unsaturated lactone ring. To this end, **12** was treated with acryloyl chloride to furnish the corresponding acrylate. However, the yield was low. In view of this, we made use of another recently proposed alternative. Alcohol **12** was treated with cinnamoyl chloride[18] to provide cinnamate **13** with good yield. Ester **13** proved to be unresponsive to RCM using the standard, first-generation ruthenium complex $PhCH{=}RuCl_2(PCy_3)_2$ but gave the desired lactone **14** in the presence of the second-generation, carbene-modified ruthenium catalyst **C**.[8] Finally, acid-catalyzed cleavage[19] of all silyl protecting groups in **14** gave lactone **1** in a very satisfactory 75% yield. However, the NMR data of synthetic **1** proved to be different from those published for the natural product.[4,20] The optical rotation was also markedly different in value and opposite in sign. Stereoisomer **2** was then synthesized from intermediate **11** along the same methodology using the appropriate chiral allyl borane (Scheme 2). Once again, however, the spectral data and the optical rotation of synthetic **2** proved to be different from those of the natural product.[20,21]

These results led us to conjecture whether the assigned configuration at C-7 was erroneous. We thus decided to synthesize compounds **3** and **4** (Figure 2), epimeric of each other at C-5 and opposite in their configuration at C-7 to lactones **1** and **2**, respectively. The same methodology used for the latter compounds was applied again here, with the appropriate chiral allyl borane being selected in each case (details of these syntheses can be found in the Supporting Information). However, we experienced a new failure in that the data of synthetic compounds **3** and **4** proved to be different from those of the natural product.[20,22]

At this point, we started having serious doubts about the validity of some of the data presented in the original paper.[4] We thus subjected them to a careful reexamination. The NMR data of this family of compounds first

(6) (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. (g) Falomir, E.; Murga, J.; Ruiz, P.; Carda, M.; Marco, J. A.; Pereda-Miranda, R.; Fragoso-Serrano, M.; Cerda-García-Rojas, C. M. *J. Org. Chem*. **2003**, *68*, 5672−5676. (h) Díaz-Oltra, S.; Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2004**, *60*, 2979−2985.

(7) For recent synthetic methodologies aimed at the stereoselective creation of 1,3-polyol segments, see: (a) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635−645. (b) Palomo, C.; Aizpurua, J. M.; Urchegi, R.; García, J. M. *J. Org. Chem*. **1993**, *58*, 1646−1648. (c) Rychnovsky, S. D.; Hoye, R. C. *J. Am. Chem. Soc*. **1994**, *116*, 1753−1765. (d) Mori, Y.; Asai, M.; Okumura, A.; Furukawa, H. *Tetrahedron* **1995**, *51*, 5299−5314. (e) Schneider, C.; Rehfeuter, M. *Chem. Eur. J*. **1999**, *5*, 2850−2858. (f) Trieselmann, T.; Hoffmann, R. W. *Org. Lett*. **2000**, *2*, 1209−1212. (g) Sarraf, S. T.; Leighton, J. L. *Org. Lett*. **2000**, *2*, 3205−3208. (h) Hunter, T. J.; O'Doherty, G. A. *Org. Lett*. **2001**, *3*, 2777−2780. (i) Cossy, J.; BouzBouz, S.; Pradaux, F.; Willis, C.; Bellosta, V. *Synlett* **2002**, 1595−1606. (j) Evans, D. A.; Côté, B.; Coleman, P. J.; Connell, B. T. *J. Am. Chem. Soc*. **2003**, *125*, 10893−10898.

(8) Trnka, T.; Grubbs, R. H. *Acc. Chem. Res*. **2001**, *34*, 18−29.

(9) Preliminary communication: García-Fortanet, J.; Murga, J.; Carda, M.; Marco, J. A. *Org. Lett*. **2003**, *5*, 1447−1449.

(10) (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.

(11) Allylation under Keck and related conditions (ref 12) was unsuccessful here (extremely slow reaction). The use of the Duthaler−Hafner allylation reagent (ref 13) was discontinued because of its very high price.

(12) (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.

(13) Duthaler, R. O.; Hafner, A. *Chem. Rev*. **1992**, *92*, 807−832.

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

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

(16) Chomatographic separation of diastereomers (**7** + epimer) proved to be difficult. After desilylation, separation was much easier and the pure diol **8** was then resilylated to **9**.

(17) This was shown by means of ^{13}C NMR and NOE measurements on the acetonide of diol **8**. See: Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res*. **1998**, *31*, 9−17.

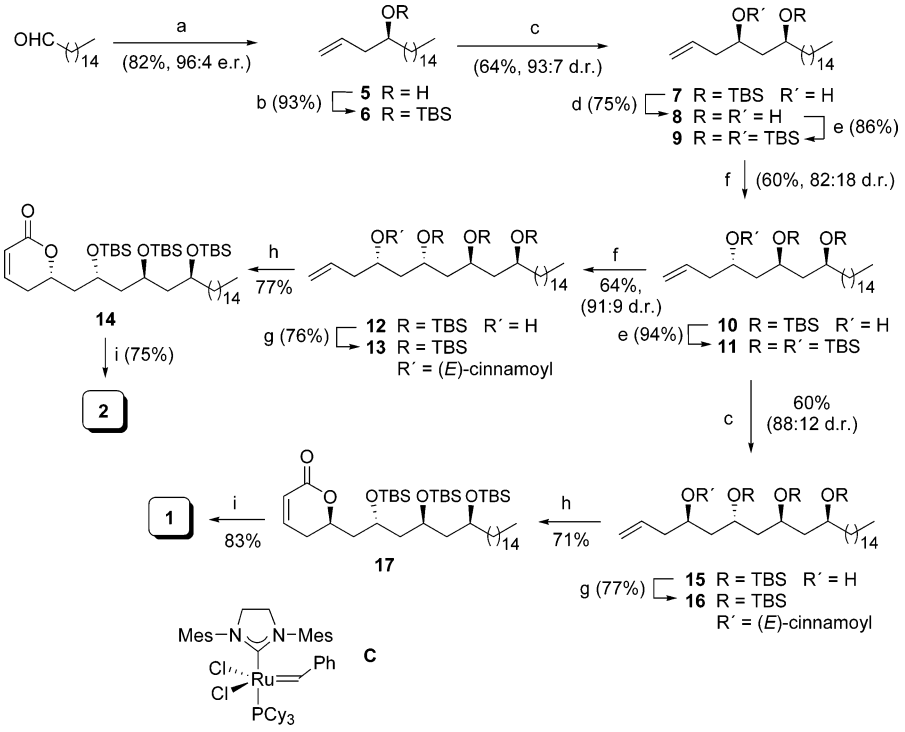
(18) Ramachandran, P. V.; Chandra, J. S.; Reddy, M. V. R. *J. Org. Chem*. **2002**, *67*, 7547−7550.

(19) The 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.

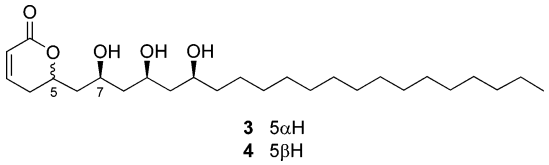
(20) Comparison with NMR spectra of the authentic sample showed clear differences, most particularly in the ^{13}C signals around 70 and 40 ppm (see Supporting Information of this paper and Supporting Information to ref 9).

(21) After our preliminary communication (ref 9) had appeared, a second report on the synthesis of the same two compounds by means of the same retrosynthetic concept was published: BouzBouz, S.; Cossy, J. *Tetrahedron Lett*. **2003**, *44*, 4471−4473.

SCHEME 2. Stereoselective Synthesis of Structures 1 and 2[a]



[a] Reagents and conditions: (a) allylBIpc$_2$ from (+)-DIP−Cl and allylmagnesium bromide, Et$_2$O, −100 °C. (b) TBSCl, DMF, imidazole, rt. (c) O$_3$, CH$_2$Cl$_2$, −78 °C, then PPh$_3$, rt, then allylBIpc$_2$ from (+)-DIP−Cl, Et$_2$O, −100 °C. (d) TBAF, THF, rt, then chromatographic separation of the two diastereomers. (e) TBSOTf, 2,6-lutidine, rt, CH$_2$Cl$_2$. (f) O$_3$, CH$_2$Cl$_2$, −78 °C, then PPh$_3$, rt, then allylBIpc$_2$ from (−)-DIP−Cl, Et$_2$O, −100 °C, then chromatographic separation of the two diastereomers. (g) (*E*)-Cinnamoyl chloride, NEt$_3$, cat. DMAP, CH$_2$Cl$_2$, rt. (h) 10% catalyst **C**, CH$_2$Cl$_2$, Δ. (i) PPTS, aq MeOH, 70 °C. Abbreviations and acronyms: TBS = *tert*-butyldimethylsilyl; DIP−Cl = diisopinocampheylboron chloride; TBAF = tetra-*n*-butylammonium fluoride hydrate; er, enantiomeric ratio; dr, diastereomeric ratio.

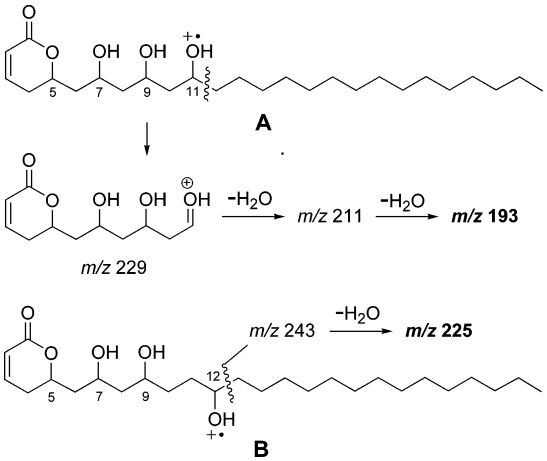


3 5α*H*
4 5β*H*

FIGURE 2. Two stereoisomers of the structures initially proposed for passifloricin A.

caught our attention. As a matter of fact, the ^{1}H and ^{13}C NMR spectra of the stereoisomeric lactones **1**−**4** were very similar (see Supporting Information). Spin decoupling was not overly helpful in assigning 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 two-dimensional measurements, these were the methylene signals of the CH(OR)**CH$_2$**CH(OR) fragments (C-6/C-8/C-10 in **1**−**4**). This finding suggested that the natural lactone had only two moieties of this class. Consequently, one of the hydroxyl groups was misplaced.

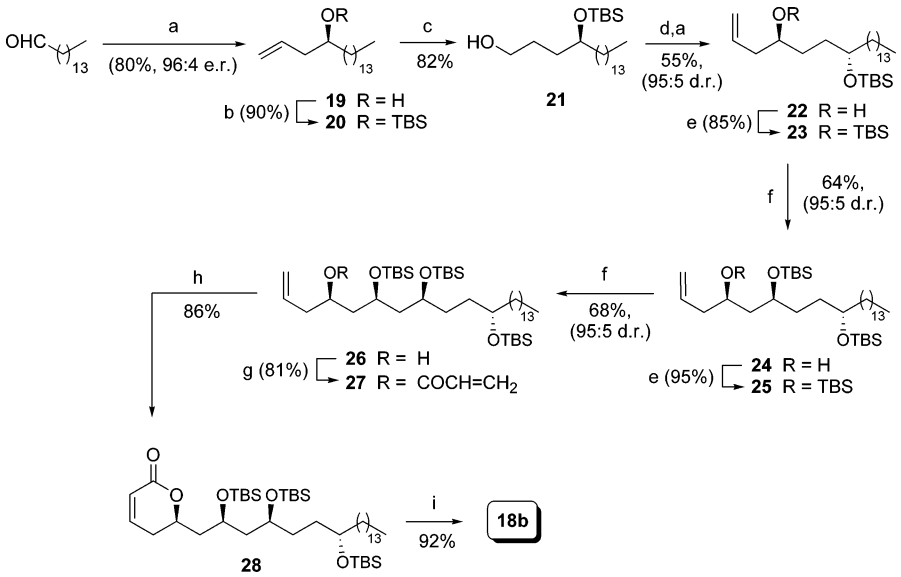
SCHEME 3. Ion Fragmentations in the Mass Spectra of Structures A and B



This finding alone, however, opened too many structural possibilities. 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 synthetic compounds **1**−**4**, which can be represented by the generic structure **A** (Scheme 3), 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

(22) Compound **3** is the enantiomer of a natural lactone isolated from *Eupatorium pilosum* (Herz, W.; Ramakrishnan, G. *Phytochemistry* **1978**, *17*, 1327−1332). The absolute configuration of the natural compound has been established by means of total synthesis (Nakata, T.; Suenaga, T.; Nakashima, K.; Oishi, T. *Tetrahedron Lett.* **1989**, *30*, 6529−6532). The spectral properties of synthetic **3** were found to be identical with those published for the natural product (see Supporting Information).

SCHEME 4. Stereoselective Synthesis of Compound 18b (Passifloricin A)[a]



[a] Reagents and conditions: (a) allylBIpc$_2$ from (+)-DIP−Cl and allylmagnesium bromide, Et$_2$O, −100 °C. (b) TBSCl, DMF, imidazole, rt. (c) 9-BBN, THF, rt, then H_2O_2, NaOH, EtOH, 50 °C. (d) Swern oxidation. (e) TBSOTf, 2,6-lutidine, rt, CH_2Cl_2. (f) O_3, CH_2Cl_2, −78 °C, then PPh_3, rt, then allylBIpc$_2$ from (+)-DIP−Cl, Et$_2$O, −100 °C, then chromatographic separation of the two diastereomers. (g) Acryloyl chloride, EtN*i*Pr$_2$, CH_2Cl_2, −78 °C. (h) 10% PhCH=RuCl$_2$(PCy$_3$)$_2$, CH_2Cl_2, Δ. (i) PPTS, aq MeOH, 70 °C. For abbreviations and acronyms, see Scheme 2.

A. This latter peak was mechanistically explained, as shown in Scheme 3, by invoking the known tendency of alcohol parent peaks to undergo α-cleavage with charge retention at the oxygen-bearing fragment (protonated carbonyl ion).[23] 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 211 were also visible although weak). 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 one hand and to account for the aforementioned NMR features on the other, we reasoned that the hydroxyl at C-11 in generic structure **A** should be shifted to C-12 as in **B** (Scheme 3). Assuming that this alternative structure was a reasonable possibility for passifloricin A, we decided to undertake its synthesis.

We started out with the assumption of the presence of a *syn*-1,3-diol moiety in structure **B**. With this structural fragment fixed, the other stereogenic centers were allowed to vary. 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. On the basis of this reasoning, the four stereoisomeric structures **18a**−**d** were our synthetic targets (Figure 3).

The synthetic concept for structures **18a**−**d** (Scheme 4) deviates only slightly from that proposed for compounds **1**−**4** and relies once again upon Brown's asymmetric allylations. The only difference is that, due to the one-carbon shift of the first hydroxyl function made, the initial asymmetric allylation was followed by hydroboration−oxidation of the olefinic bond, instead of oxidative cleavage. The unsaturated lactone ring was formed,

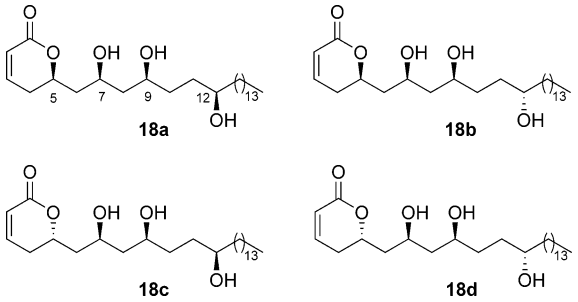


FIGURE 3. Alternative stereoisomeric structures for passifloricin A or its enantiomer.

as previously, via RCM. Only the synthesis of stereoisomer **18b**, which finally proved to be identical to passifloricin A, is described hereafter (details of the synthesis of the other three stereoisomers can be found in Supporting Information).[24]

n-Pentadecanal[25] was reacted with the B-allyl diisopinocampheylborane prepared from allylmagnesium bromide and (+)-DIP−Cl.[10] This gave homoallyl alcohol **19** as a 96:4 enantiomeric mixture (Scheme 4), as judged from NMR analysis of the Mosher ester. Protection of the hydroxyl group as the TBS derivative was followed by hydroboration to yield primary alcohol **21**. Swern oxidation of the latter gave an intermediate γ-silyloxy aldehyde which, without further chromatographic purification, was subjected to asymmetric allylation with the same reagent as above. This gave homoallyl alcohol **22**, which was then silylated to **23**. Ozonolysis of the olefinic bond in the latter compound was followed by asymmetric allylation with

(23) McLafferty, F. W.; Tureček, F. *Interpretation of Mass Spectra*, 4th ed.; University Science Books: Mill Valley, CA, 1993; Chapter 9.

(24) Preliminary communication: Murga, J.; García-Fortanet, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2003**, *44*, 7909−7912. The complete synthetic work and the results of the biological evaluations will be a part of the projected Ph.D. Thesis of J.G.-F.

(25) Freshly prepared by PCC oxidation of *n*-pentadecanol.

the same reagent as above. This afforded the protected triol **24**, which was silylated to **25** and subjected once more to the same ozonolysis−allylation protocol to yield alcohol **26**. The latter was then treated with acryloyl chloride to furnish in good yield the corresponding acrylate **27**. The latter was reactive enough as to undergo RCM with the less expensive ruthenium catalyst PhCH=$RuCl_2(PCy_3)_2$ with formation of the unsaturated lactone **28**. Acid-catalyzed cleavage of all the silyl protecting groups in **28** afforded lactone **18b** in a 92% yield. The NMR data of **18b** proved to be identical to those reported for the natural product.[4,26] Furthermore, treatment of **18b** with acetone and an acid catalyst gave only one acetonide, the NMR features of which (see Supporting Information) revealed its identity with those of the acetonide prepared from the natural product.[4]

Conclusion

We have performed a stereoselective, asymmetric synthesis of the natural lactone passifloricin A and shown it to be **18b**. 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 sizable amounts of the compound and of several isomers thereof for the evaluation of its biological properties.[5,24] The latter are now being determined and will be reported in a future communication.

Experimental Section

(*S*)-Octadec-1-en-4-ol (19). Allylmagnesium bromide (commercial 1 M solution in Et_2O, 7.5 mL, 7.5 mmol) was added dropwise under N_2 via syringe to a solution of (+)-DIP−Cl (2.89 g, 9 mmol) in dry Et_2O (40 mL) cooled in a dry ice−acetone bath. After replacing the latter by an ice bath, the mixture was stirred for 1 h. The solution was then allowed to stand, which caused precipitation of magnesium chloride. The supernatant solution was then carefully transferred to another flask via cannula. After the flask was cooled at −100 °C, a solution of freshly prepared[25] pentadecanal (1.36 g, 6 mmol) in dry Et_2O (15 mL) was added dropwise via syringe. The resulting solution was further stirred at the same temperature for 1 h. The reaction mixture was then quenched through addition of phosphate pH 7 buffer solution (40 mL), MeOH (40 mL), and 30% H_2O_2 (20 mL). After stirring for 30 min, the mixture was poured onto saturated aqueous $NaHCO_3$ and worked up (extraction with Et_2O). Column chromatography on silica gel (hexanes−EtOAc, 9:1) afforded **19** (1.28 g, 80%, 96:4 mixture of enantiomers as estimated via the Mosher ester): solid, mp 47−49 °C (from hexanes); $[\alpha]_D$ −2.9 (*c* 1.9, $CHCl_3$); ^{1}H NMR (500 MHz) δ 5.80 (m, 1H), 5.15−5.10 (m, 2H), 3.60 (m, 1H), 2.28 (m, 1H), 2.13 (m, 1H), 1.70 (br s, 1H, OH), 1.50−1.40 (m, 3H), 1.40−1.20 (br m, 23H), 0.87 (t, 6.5 Hz, 3H); ^{13}C NMR (125 MHz) δ 134.9, 70.7 (CH), 117.8, 41.9, 36.8, 31.9, 29.7 (several overlapped peaks), 29.3, 25.6, 22.6 (CH_2), 14.0 (CH_3); IR ν_{max} 3330 (br, OH) cm^{-1}; HR EIMS *m*/*z* (% rel intensity) 227.2338 ($M^+ - C_3H_5$, 100), 125 (24), 111 (53), 97 (82), 83 (85). Calcd for $C_{18}H_{36}O - C_3H_5$, 227.2375.

(*S*)-4-(*tert*-Butyldimethylsilyloxy)octadec-1-ene (20). Alcohol **19** (1.21 g, 4.5 mmol) was dissolved under N_2 in dry DMF (30 mL) and treated sequentially with imidazole (460 mg, 6.75 mmol) and TBSCl (0.98 g, 6.45 mmol). The reaction mixture was then stirred for 18 h at room temperature and worked up (extraction with Et_2O). Column chromatography on silica gel (hexanes−EtOAc, 99:1) afforded **20** (1.55 g, 90%): oil; $[\alpha]_D$ −7.2 (*c* 2, $CHCl_3$); ^{1}H NMR (500 MHz) δ 5.82 (m, 1H), 5.05−5.00 (m, 2H), 3.70 (quint, 6 Hz, 1H), 2.20 (m, 2H), 1.50−1.40 (m, 3H), 1.35−1.20 (br m, 23H), 0.90 (s, 9H), 0.88 (t, 6.5 Hz, 3H), 0.06 (s, 6H); ^{13}C NMR (125 MHz) δ 18.2 (C), 135.6, 72.1 (CH), 116.5, 42.0, 36.9, 32.0, 29.8, 29.7 (several overlapped peaks), 29.4, 25.4, 22.7 (CH_2), 26.0 (x3), 14.1, −4.4, −4.5 (CH_3); HR FABMS *m*/*z* 383.3656 ($M + H^+$). Calcd for $C_{24}H_{51}OSi$, 383.3709.

(*S*)-4-(*tert*-Butyldimethylsilyloxy)octadecanol (21). A solution of olefin **20** (1.53 g, 4 mmol) in dry THF (40 mL) was treated under N_2 with 9-BBN (12 mL of a 0.5 M THF solution, 6 mmol). The reaction mixture was stirred for 18 h at room temperature and then quenched by addition of MeOH (8 mL), 6 M aqueous NaOH (3 mL), and 30% H_2O_2 (5 mL). The resulting mixture was then stirred at 50 °C for 1 h and worked up (extraction with EtOAc). Column chromatography on silica gel (hexanes−EtOAc, 19:1) afforded **21** (1.31 g, 82%): oil; $[\alpha]_D$ +3.0 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz) δ 3.70 (quint, 6 Hz, 1H), 3.60 (m, 2H), 2.30 (br s, 1H, OH), 1.60 (m, 2H), 1.53 (m, 2H), 1.45 (m, 2H), 1.35−1.20 (br m, 25H), 0.89 (s, 9H), 0.88 (t, overlapped, 3H), 0.05 (s, 6H); ^{13}C NMR (125 MHz) δ 18.1 (C), 72.2 (CH), 63.2, 36.7, 33.4, 32.0, 29.8, 29.7 (several overlapped peaks), 29.6, 29.4, 28.2, 25.4, 22.7 (CH_2), 25.9 (x3), 14.1, −4.5 (x2) (CH_3); IR ν_{max} 3340 (br, OH) cm^{-1}; HR FABMS *m*/*z* 401.3810 ($M + H^+$). Calcd for $C_{24}H_{53}O_2Si$, 401.3814.

(4*S*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)henicos-1-en-4-ol (22). DMSO (525 μL, 7.5 mmol) was dissolved under N_2 in dry CH_2Cl_2 (7 mL), cooled to −78 °C, and treated with oxalyl chloride (328 μL, 3.75 mmol). After the mixture was stirred at this temperature for 5 min, a solution of **21** (1.2 g, 3 mmol) in dry CH_2Cl_2 (3 mL) was added dropwise, followed by triethylamine (2.1 mL, 15 mmol). The reaction mixture was stirred for 15 min at −78 °C and then for an additional 60 min at 0 °C. Workup (extraction with CH_2Cl_2) and evaporation in vacuo provided a crude aldehyde that was subjected to allyboration with (+)-DIP−Cl as described above (for weight calculations, the yield of the oxidation was assumed to be quantitative). Workup as above and column chromatography on silica gel (hexanes−EtOAc, 19:1) furnished compound **22** (95:5 mixture of diastereomers, after chromatographic separation 727 mg, 55% overall): oil; $[\alpha]_D$ +1.3 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz) δ 5.83 (m, 1H), 5.15−5.10 (m, 2H), 3.70 (quint, 6 Hz, 1H), 3.60 (m, 1H), 2.40 (br s, 1H, OH), 2.30−2.20 (m, 2H), 1.65−1.40 (m, 6H), 1.35−1.20 (br m, 24H), 0.90 (s, 9H), 0.88 (t, overlapped, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz) δ 18.1 (C), 135.1, 72.4, 71.2 (CH), 42.0, 36.7, 33.2, 32.4, 32.0, 29.8, 29.7 (several overlapped peaks), 29.6, 29.4, 25.4, 22.7 (CH_2), 25.9 (x3), 14.1, −4.5 (x2) (CH_3); IR ν_{max} 3430 (br, OH) cm^{-1}; HR FABMS *m*/*z* 423.4027 ($M + H^+ - H_2O$). Calcd for $C_{27}H_{57}O_2Si - H_2O$, 423.4022.

(4*S*,7*S*)-4,7-Bis(*tert*-butyldimethylsilyloxy)henicos-1-ene (23). Alcohol **22** (705 mg, 1.6 mmol) was dissolved under N_2 in dry CH_2Cl_2 (8 mL) and treated sequentially with 2,6-lutidine (280 μL, 2.4 mmol) and TBSOTf (460 μL, 2 mmol). The reaction mixture was then stirred for 1 h at room temperature and worked up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexanes−EtOAc, 99:1) afforded **23** (755 mg, 85%): oil; $[\alpha]_D$ −3 (*c* 2.1, $CHCl_3$); ^{1}H NMR (500 MHz) δ 5.82 (m, 1H), 5.10−5.00 (m, 2H), 3.68 (m, 1H), 3.62 (m, 1H), 2.20 (t, 6.5 Hz, 2H), 1.60−1.50 (m, 2H), 1.50−1.20 (br m, 28H), 0.90 (s, 9H), 0.89 (s, 9H), 0.88 (t, overlapped, 3H), 0.05 (s, 6H), 0.04 (s, 6H); ^{13}C NMR (125 MHz) δ 18.2 (x2) (C), 135.4, 72.7, 72.5 (CH), 116.7, 42.1, 37.2, 32.7, 32.5, 32.0, 29.9, 29.7 (several overlapped peaks), 29.5, 25.4, 22.7 (CH_2), 26.0 (x3), 25.9 (x3), 14.1, −4.4 (x3), −4.5 (CH_3); HR EIMS *m*/*z* (%

(26) The reported numerical value of the optical rotation of passifloricin A is very different from that found by us for **18b**. 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 natural products were then found to have almost identical optical rotations (see Supporting Information).

rel intensity) 497.4187 ($M^+ - t$Bu, 28), 415 (14), 381 (80), 365 (48), 73 (100). Calcd for $C_{33}H_{70}O_2Si_2 - t$Bu, 497.4204.

(4*R*,6*S*,9*S*)-6,9-Bis(*tert*-butyldimethylsilyloxy)tricos-1-en-4-ol (24). Compound **23** (721 mg, 1.3 mmol) was dissolved in dry CH_2Cl_2 (12 mL) and cooled to −78 °C. A stream of ozone-oxygen was bubbled through the solution until persistence of the bluish color. Dry N_2 was then bubbled through the solution for 10 min at the same temperature. After addition of PPh_3 (682 mg, 2.6 mmol), the solution was left to stir at room temperature for 2 h and then worked up (extraction with CH_2Cl_2). Solvent removal gave a solid material, which was washed three times with cold pentane (3 × 10 mL). The solid (Ph_3PO) was discarded, and the organic phase was evaporated in vacuo to yield an oily product that was used as such in the asymmetric allylation with (+)-DIP−Cl (for weight calculations, the yield of the ozonolysis step was assumed to be quantitative). Workup as above and column chromatography on silica gel (hexanes−EtOAc, 19:1) provided compound **24** (95:5 mixture of diastereomers, after chromatographic separation 499 mg, 64% overall): oil; $[\alpha]_D$ +14.2 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz) δ 5.83 (m, 1H), 5.15−5.05 (m, 2H), 3.91 (m, 1H), 3.80 (m, 1H), 3.62 (quint, 6 Hz, 1H), 3.10 (br s, 1H, OH), 2.23 (t, 6.5 Hz, 2H), 1.65−1.40 (m, 6H), 1.35−1.20 (br m, 26H), 0.90 (s, 9H), 0.88 (s, 9H), 0.87 (t, overlapped, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (125 MHz) δ 18.1, 18.0 (C), 134.9, 73.1, 72.3, 70.1 (CH), 117.4, 42.4, 42.2, 37.0, 33.2, 32.0, 31.7, 29.9, 29.7 (several overlapped peaks), 29.4, 25.3, 22.7 (CH_2), 26.0 (x3), 25.9 (x3), 14.1, −4.0, −4.4, −4.5, −4.7 (CH_3); IR ν_{max} 3480 (br, OH) cm^{-1}; HR EIMS *m*/*z* (% rel intensity) 541.4410 ($M^+ - t$Bu, 1), 409 (100), 341 (48), 145 (64). Calcd for $C_{35}H_{74}O_3Si_2 - t$Bu, 541.4472.

(4*R*,6*S*,9*S*)-4,6,9-Tris(*tert*-butyldimethylsilyloxy)tricos-1-ene (25). Alcohol **24** (479 mg, 0.8 mmol) was subjected to silylation as reported above for **23**. Workup as above and column chromatography on silica gel (hexanes−EtOAc, 19:1) gave compound **25** (542 mg, 95%): oil; $[\alpha]_D$ −4.3 (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz) δ 5.82 (m, 1H), 5.05−5.00 (m, 2H), 3.79 (m, 2H), 3.62 (quint, 6 Hz, 1H), 2.28 (m, 1H), 2.18 (m, 1H), 1.65−1.50 (m, 3H), 1.45−1.35 (m, 2H), 1.35−1.20 (br m, 27H), 0.90 (br s, 27H), 0.88 (t, overlapped, 3H), 0.07 (s, 3H), 0.06 (s, 6H), 0.05 (s, 6H), 0.03 (s, 3H); ^{13}C NMR (125 MHz) δ 18.2, 18.1 (x2) (C), 135.1, 72.6, 69.8, 69.4 (CH), 117.0, 44.6, 42.1, 37.1, 32.6, 32.3, 32.0, 29.9, 29.7 (several overlapped peaks), 29.4, 25.4, 22.7 (CH_2), 26.0 (x6), 25.9 (x3), 14.1, −4.3 (x3), −4.4 (x2), −4.5 (CH_3); HR EIMS *m*/*z* (% rel intensity) 655.5369 ($M^+ - t$Bu, 8), 523 (12), 455 (32), 381 (60), 185 (100), 73 (68). Calcd for $C_{41}H_{88}O_3Si_3 - t$Bu, 655.5337.

(4*R*,6*R*,8*S*,11*S*)-6,8,11-Tris(*tert*-butyldimethylsilyloxy)-pentacos-1-en-4-ol (26). Olefin **25** (535 mg, 0.75 mmol) was subjected to the same ozonolysis/allylation sequence as described above for **24**. Workup as above and column chromatography on silica gel (hexanes−EtOAc, 19:1) afforded alcohol **26** (95:5 mixture of diastereomers, after chromatographic separation 386 mg, 68% overall): oil; $[\alpha]_D$ +20.9 (*c* 1.5, $CHCl_3$); ^{1}H NMR (500 MHz) δ 5.82 (m, 1H), 5.15−5.05 (m, 2H), 4.07 (m, 1H), 3.81 (m, 1H), 3.70 (m, 1H), 3.62 (quint, 6 Hz, 1H), 3.30 (br s, 1H, OH), 2.30−2.20 (m, 2H), 1.80−1.70 (m, 2H), 1.55−1.40 (m, 4H), 1.35−1.20 (br m, 28H), 0.90 (s, 9H), 0.88 (s, 18H), 0.88 (t, overlapped, 3H), 0.12 (s, 6H), 0.05 (s, 3H), 0.04 (s, 6H), 0.03 (s, 3H); ^{13}C NMR (125 MHz) δ 18.1, 18.0, 17.9 (C), 135.0, 72.4, 70.8, 70.3, 69.6 (CH), 117.4, 45.6, 42.5, 42.3, 37.1, 33.2, 32.0, 31.9, 29.9, 29.7 (several overlapped peaks), 29.4, 25.4, 22.7 (CH_2), 26.0 (x3), 25.9 (x3), 25.8 (x3), 14.1, −3.9, −4.0, −4.4 (x2), −4.5 (x2) (CH_3); IR ν_{max} 3500 (br, OH) cm^{-1}; HR EIMS *m*/*z* (% rel intensity) 699.5545 ($M^+ - t$Bu, 1), 567 (17), 435 (55), 381 (53), 341 (36), 73 (100). Calcd for $C_{43}H_{92}O_4Si_3 - t$Bu, 699.5599.

(4*R*,6*R*,8*S*,11*S*)-6,8,11-Tris(*tert*-butyldimethylsilyloxy)-pentacos-1-en-4-yl Acrylate (27). Alcohol **26** (379 g, 0.5 mmol) was dissolved under N_2 in dry CH_2Cl_2 (20 mL), cooled to −78 °C, and treated sequentially with ethyl diisopropylamine (1.3 mL, 7.5 mmol) and acryloyl chloride (400 μL, 5 mmol). The reaction mixture was stirred for 2 h at −78 °C and then worked up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexanes−EtOAc, 19:1) afforded ester **27** (329 mg, 81%): amorphous solid; $[\alpha]_D$ −13 (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz) δ 6.39 (dd, 17.3, 1.5 Hz, 1H), 6.09 (dd, 17.3, 10.5 Hz, 1H), 5.80−5.70 (m, 2H), 5.15 (m, 1H), 5.10−5.05 (m, 2H), 3.80−3.75 (m, 2H), 3.60 (quint, 5.5 Hz, 1H), 2.40 (m, 1H), 2.33 (m, 1H), 1.82 (ddd, 14, 8, 4.8 Hz, 1H), 1.75 (ddd, 14, 6.6, 4.8 Hz, 1H), 1.65−1.40 (m, 5H), 1.35−1.20 (br m, 27H), 0.90 (s, 9H), 0.88 (s, 18H), 0.88 (t, overlapped, 3H), 0.07 (s, 3H), 0.05 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz) δ 165.4, 18.2, 18.1, 18.0 (C), 133.5, 128.9, 72.7, 70.7, 69.5, 67.0 (CH), 130.3, 117.9, 44.9, 41.5, 39.2, 37.2, 32.5, 32.0, 29.9, 29.7 (several overlapped peaks), 29.4, 25.3, 22.7 (CH_2), 26.0 (x3), 25.9 (x6), 14.1, −4.3 (x3), −4.4 (x2), −4.5 (CH_3); IR ν_{max} 1729 (C=O) cm^{-1}; FABMS *m*/*z* 811 ($M + H^+$); HR EIMS *m*/*z* (% rel intensity) 753.5723 ($M^+ - t$Bu, 2), 381 (100), 343 (56). Calcd for $C_{46}H_{94}O_5Si_3 - t$Bu, 753.5704.

(*R*)-5,6-Dihydro-6-[(2*R*,4*S*,7*S*)-2,4,7-tris(*tert*-butyldimethylsilyloxy)henicosyl]pyran-2-one (28). Compound **27** (324 mg, 0.4 mmol) was dissolved under N_2 in dry, degassed CH_2Cl_2 (40 mL) and treated with ruthenium catalyst PhCH=$RuCl_2(PCy_3)_2$ (32 mg, 0.04 mmol). The mixture was heated at reflux until consumption of the starting material (ca. 3 h, *TLC monitoring!*). Solvent removal in vacuo and column chromatography on silica gel (hexanes−EtOAc, 19:1) furnished lactone **28** (270 mg, 86%): amorphous solid; $[\alpha]_D$ +23.4 (*c* 1.9, $CHCl_3$); ^{1}H NMR (500 MHz) δ 6.85 (m, 1H), 5.99 (dd, 9.7, 2 Hz, 1H), 4.60 (m, 1H), 4.00 (quint, 6 Hz, 1H), 3.76 (m, 1H), 3.62 (quint, 6 Hz, 1H), 2.39 (dt, 18, 5 Hz, 1H), 2.29 (ddt, 18, 11.5, 2.5 Hz, 1H), 2.00 (dt, 14, 6 Hz, 1H), 1.85 (dt, 14, 6 Hz, 1H), 1.70−1.40 (m, 6H), 1.35−1.20 (br m, 26H), 0.89 (s, 18H), 0.88 (s, 9H), 0.88 (t, overlapped, 3H), 0.07 (s, 3H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (125 MHz) δ 164.0, 18.0 (x 2), 17.9 (C), 144.6, 121.6, 75.1, 72.4, 69.5, 66.3 (CH), 44.4, 41.8, 37.0, 32.8, 32.2, 31.9, 29.9, 29.7 (several overlapped peaks), 29.3, 25.3, 22.7 (CH_2), 25.9 (x6), 25.8 (x3), 14.1, −4.2, −4.4 (x2), −4.5 (x2), −4.6 (CH_3); IR ν_{max} 1739 (C=O) cm^{-1}; HR FABMS *m*/*z* 725.5376 ($M^+ - t$Bu). Calcd for $C_{44}H_{90}O_5Si_3 - t$Bu, 753.5391.

(*R*)-5,6-Dihydro-6-[(2*S*,4*S*,6*S*)-2,4,6-trihydroxyhenicosyl]pyran-2-one, Passifloricin A (18b). Compound **28** (235 mg, 0.3 mmol) was dissolved in MeOH (15 mL) and treated with PPTS (15 mg, 0.06 mmol) and water (0.15 mL). The mixture was then heated at reflux for 18 h, cooled, and neutralized by addition of solid $NaHCO_3$. After being filtered, the solution was evaporated in vacuo, and the oily residue was subjected to column chromatography on silica gel (EtOAc−MeOH, 19:1). This yielded lactone **18b** (121 mg, 92%): colorless solid, mp 103−106 °C (from EtOAc−MeOH), lit.[4] for passifloricin A mp 97 °C; $[\alpha]_D$ +28.9 (*c* 0.8, MeOH), lit.[4] for passifloricin A $[\alpha]_D$ +123.45 (*c* 0.11, MeOH); $[\alpha]_D$ +33.3 (*c* 0.8, $CHCl_3$) for **18b**; $[\alpha]_D$ +34.1 (*c* 0.5, $CHCl_3$) for a sample of natural passifloricin A; ^{1}H NMR (500 MHz) δ 6.89 (ddd, 9.5, 5.5, 3 Hz, 1H), 6.00 (br d, 9.5 Hz, 1H), 4.66 (sext, 5.5 Hz, 1H), 4.30 (br s, OH, 1H), 4.11 (m, 1H), 3.95 (m, 1H), 3.64 (m, 1H), 2.50−2.40 (m, 2H), 2.04 (dt, J = 14, 7.5 Hz, 1H), 1.80 (dt, J = 14, 5.5 Hz, 1H), 1.70−1.50 (br m, 4H), 1.50−1.40 (m, 2H), 1.35−1.20 (br m, 28H), 0.87 (t, 7 Hz, 3H); ^{13}C NMR (125 MHz) δ 164.4 (C), 145.5, 121.2, 76.2, 72.5, 71,9, 69.5 (CH), 42.8, 42.4, 37.5, 34.1, 32.7, 32.0, 29.7 (several overlapped peaks), 29.5, 29.4, 25.9, 22.7 (CH_2), 14.1 (CH_3); IR ν_{max} 3260 (br, OH), 1715 (C=O) cm^{-1}; HR EIMS *m*/*z* (rel intensity) 422.3411 ($M^+ - H_2O$, 2), 404 ($M^+ - 2H_2O$, 6), 267 (32), 225 (100), 141 (66). Calcd for $C_{26}H_{48}O_5 - H_2O$, 422.3396. The identity of natural and synthetic product was confirmed by the measurement of the NMR spectra of a mixture of both compounds.

Acetonide of Passifloricin A. Compound **18b** (13 mg, 0.03 mmol) was dissolved in acetone (800 μL) and treated with 2,2-dimethoxypropane (200 μL) and camphorsulfonic acid (5 mg). After adding a small amount of 4 Å molecular sieves, the mixture was stirred at room temperature for 3 h. After being filtered through a pad of Celite, the solution was evaporated

in vacuo and chromatographed on silica gel (hexanes−EtOAc, 1:1) to yield only an acetonide (9 mg, 65% yield): colorless oil; ^{1}H NMR (500 MHz) δ 6.83 (ddd, 9.6, 5.8, 2.5 Hz, 1H), 5.97 (br dd, 9.6, 2 Hz, 1H), 4.54 (sext, 5.5 Hz, 1H), 4.10 (m, 1H), 3.81 (m, 1H), 3.52 (m, 1H), 2.38 (ddt, J = 18.5, 11.5, 2.6 Hz, 1H), 2.30 (br dt, J = 18.5, 5 Hz, 1H), 2.00 (dt, J = 14.5, 7 Hz, 1H), 1.70 (dt, J = 14.5, 5.5 Hz, 1H), 1.60−1.35 (br m, 4H), 1.37 (3H, s), 1.36 (m, 1H), 1.31 (s, 3H), 1.30−1.20 (br m, 28H), 0.84 (t, 7 Hz, 3H); ^{13}C NMR (125 MHz) δ 164.4, 98.8 (C), 145.2, 121.5, 74.7, 71.5, 69.3, 65.1 (CH), 41.0, 37.5, 36.5, 33.2, 32.4, 31.9, 29.7 (several overlapped peaks), 29.4, 29.3, 25.9, 22.7 (CH_2), 30.2, 19.9, 14.1 (CH_3); IR ν_{max} 3300 (br, OH), 1715 (C=O) cm^{-1}.

Acknowledgment. Financial support has been granted by the Spanish Ministry of Science and Technology (Project BQU2002-00468), the AVCyT (Project Grupos03/180), and the BANCAJA-UJI Foundation (Project PI-1B2002-06). J.M. and J.G.-F. thank the Spanish Ministry of Education and Science for a Ramón y Cajal fellowship and for a FPU predoctoral fellowship, respectively. The authors further thank Prof. F. Echeverri, from the University of Antioquía, Colombia, for sending a sample of passifloricin A and copies of NMR and mass spectra thereof.

Supporting Information Available: General information about spectral measurements and experimental procedures; spectral data of compounds **1**−**6**, **8**−**17**, **18a**−**d**, as well as of the synthetic intermediates in the route toward lactones **1**−**4** and **18a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049275D