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Enantioselective allyltitanations: synthesis of the proposed structures for passifloricin A

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Abstract—The stereoselective total synthesis of the proposed structures **P1** and **P2** for passifloricin A was achieved in 12 steps from *n*-hexadecanal by using enantioselective allyltitanations and a ring closing metathesis reaction as the key steps. Both **P1** and **P2** are different from passifloricin A.

The family of passion flowers includes edible species such as *Passiflora quadrangulis*, *P. ligularis*, *P. mollisima* and *P. eludis*. In the course of their investigations of *Passiflora foetida* resin, Echeverri et al. discovered three polyketides α-pyrones, named passifloricins A, B, C. One of them, passifloricin A, presents a significant antifungal activity.[1] The structure and the relative configuration of this product were assigned through 2D NMR spectroscopic analyses. Unfortunately, it was not possible to establish the absolute configurations by X-ray diffraction as passifloricin A or its benzoate, β-bromobenzoate and acetate derivatives were not crystalline. Surprisingly, two structures were reported for passifloricin A: the δ-lactone of the (5*S*,7*S*,9*S*,11*S*)-tetrahydroxyhexacos-2-enoic acid **P1** and the δ-lactone of the (5*R*,7*S*,9*S*,11*S*)-tetrahydroxyhexacos-2-enoic acid **P2** (Fig. 1).

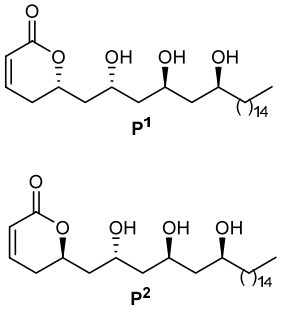
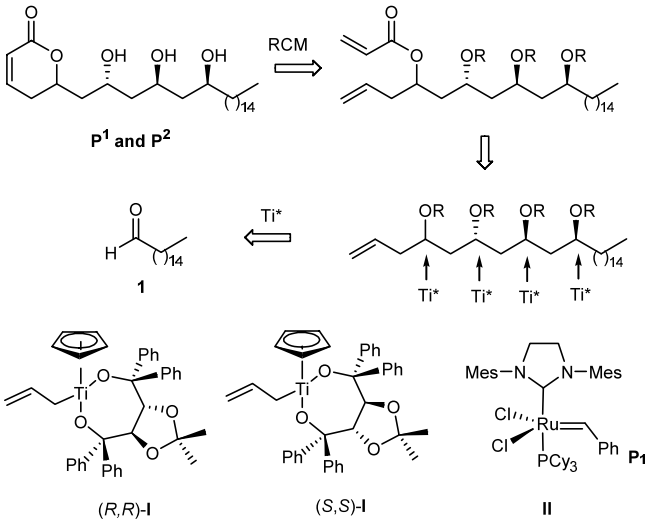


Figure 1.

Due to the antifungal properties of passifloricin A and to verify the proposed structures for this compound the synthesis of compounds **P1**[2] and **P2** were undertaken. As we have already developed efficient strategies to access *syn* and *anti* 1,3-diol units,[3] the syntheses of **P1** and **P2** were based on the use of four highly face-selective and enantioselective allytitanations applied to aldehydes to control the stereogenic centers at C5, C7, C9, C11. Furthermore, a ring-closing metathesis (RCM) reaction was envisaged to build up the unsaturated lactone. The access to **P1** and **P2** was planned according to the following retrosynthetic scheme (Scheme 1).



Scheme 1. Retrosynthetic analysis of the proposed structures for passifloricin A. Structure of the complexes (*R*,*R*)-**I**, (*S*,*S*)-**I** and of Grubbs' catalyst **II**.

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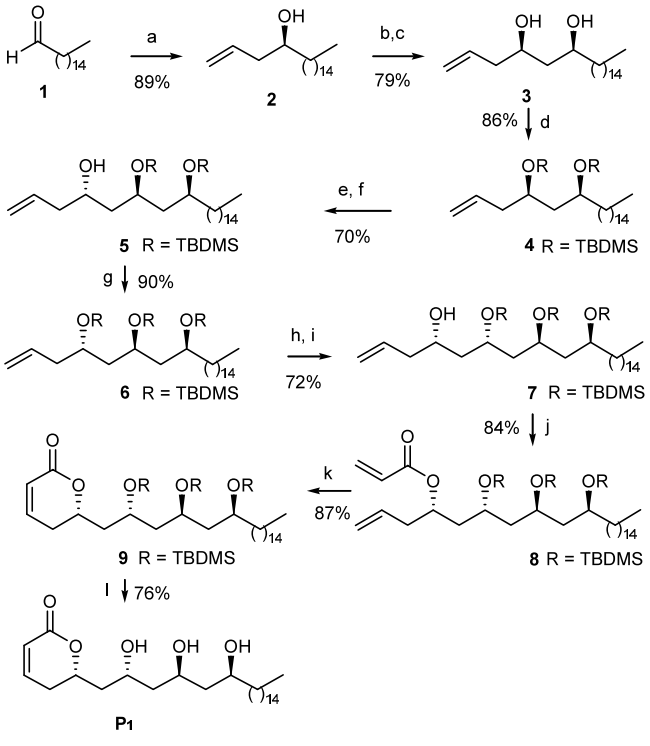
At first, the synthesis of lactone **P1** was undertaken. When *n*-hexadecanal **1** was treated with allyltitanium complex (*S*,*S*)-**I** (Scheme 1), according to the reported procedure,[4] homoallylic alcohol **2** was obtained in 89% yield with an enantiomeric excess superior to 98%[5] (Scheme 2). The absolute configuration of the newly formed stereogenic center was confirmed by using Trost's mandelic ester method.[6] After oxidative cleavage of the double bond of **2** (OsO_4/NMO, $NaIO_4$), the obtained aldehyde was not purified but directly treated with the highly face-selective (*S*,*S*)-**I** complex at −78°C and transformed to the 1,3-diol **3**[7] with an overall yield of 79% and with a diastereoselectivity of 97/3. The *syn* relative configuration of the hydroxy groups in **3** was confirmed by the analysis of the ^{13}C NMR spectra of the corresponding acetonide **3′**[8] ($\delta = 19.6$, 30.1 ppm for Me_2C, 98.2 ppm for the quaternary center).[9] It is worth noting that the transformation of **2** to **3** did not require the protection of the hydroxy group. Transformation of **3** to the corresponding *t*-butyldimethylsilyl derivative **4** by using *t*-butyldimethylsilyltrifluoromethane sulfonate (TBDMSOTf) (2,6-lutidine, CH_2Cl_2, −78°C, 86% yield) followed by the oxidative cleavage of the double bond (OsO_4,/NMO, $NaIO_4$ in acetone/H_2O) led to a sensitive aldehyde which was treated with the (*R*,*R*)-**I** complex

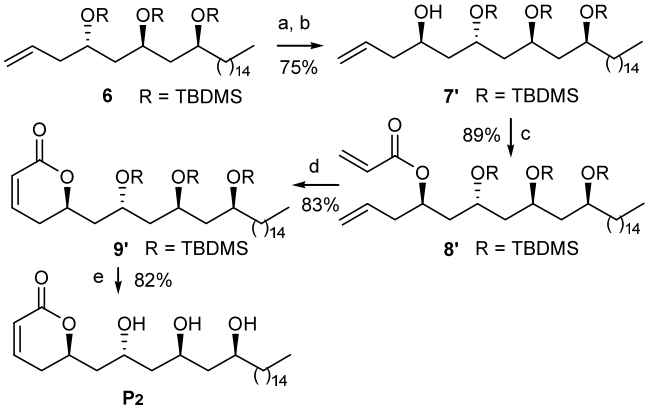


Scheme 2. *Reagents and conditions*: (a) (*S*,*S*)-**I**, ether, −78°C, 4 h; (b) OsO_4, NMO, acetone/H_2O, $NaIO_4$, 25°C; (c) (*S*,*S*)-**I**, ether, −78°C, 4 h; (d) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, −78°C; (e) OsO_4, NMO, acetone/H_2O, $NaIO_4$, 25°C; (f) (*R*,*R*)-**I**, ether, −78°C, 4 h; (g) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, −78°C; (h) OsO_4, NMO, acetone/H_2O, $NaIO_4$, 25°C; (i) (*R*,*R*)-**I**, ether, −78°C, 4 h; (j) acryloyl chloride, iPr_2NEt, CH_2Cl_2, −78°C; (k) Grubbs' catalyst **II**, CH_2Cl_2, 55°C; (l) HCl 1N, MeOH, 25°C.

(Et_2O, −78°C, 4 h) to give the allylic alcohol **5** with an overall yield of 70% for the two steps. The protection of triol **5** by using TBDMSOTf in the presence of 2,6-lutidine afforded the tris-*t*-butyldimethylsilyl derivative **6**[10] in 90% yield. After oxidative cleavage of **6** (OsO_4/NMO, $NaIO_4$), the sensitive aldehyde was treated, without any purification, with the (*R*,*R*)-**I** complex and transformed to the homoallylic alcohol **7** with a high diastereoselectivity (dr >95/5) and in 72% yield from **6**. To transform **7** to the α,β-unsaturated δ-lactone **9**, the homoallylic alcohol **7** was esterified with acryloyl chloride (iPr_2NEt, CH_2Cl_2, at −78°C, 84% yield) and the obtained ester **8** (87% yield) was treated with Grubbs' catalyst **II**[11,12] (refluxing CH_2Cl_2, 5 h) to produce the desired lactone **9** in 87% yield. In order to synthesize compound **P1**, the desilylation of **9** was achieved in the presence of HCl 1N in methanol and the desired compound **P1**[13] (Scheme 2) was isolated in 76% yield; its spectroscopic data and optical rotation did not correspond to the spectroscopic data and optical rotation of passifloricin A.[1]

Due to this result, the synthesis of **P2** was undertaken according to the same retrosynthetic scheme envisaged for **P1**. The β-oxygenated aldehyde coming from the oxidative cleavage of compound **6** was treated with the (*S*,*S*)-**I** complex. The resulting alcohol **7′** was reacted with acryloyl chloride to produce **8′** which was subjected to the ring closing metathesis reaction using Grubbs' catalyst **II** to produce **9′**. Deprotection of the hydroxy groups (1N HCl, MeOH) led to compound **P2**[14] (Scheme 3), the spectroscopic data and optical rotation of which were also different from those of passifloricin A.[1]

We are therefore forced to conclude that passifloricin A does not correspond to compounds **P1** and **P2**. However, either enantiomers as well as diastereomers can be obtained by using enantioselective allyltitanations. These highly face-selective and enantioselective reactions offer the opportunity to ascertain which diastereomer corresponds to the natural product, a task which is currently underway.



Scheme 3. *Reagents and conditions*: (a) OsO_4, NMO, acetone/H_2O, $NaIO_4$, 25°C; (b) (*S*,*S*)-**I**, ether, −78°C, 4 h; (c) acryloyl chloride, iPr_2NEt, CH_2Cl_2, −78°C; (d) Grubbs' catalyst **II**, CH_2Cl_2, 55°C; (e) HCl 1N, MeOH, 25°C.

Acknowledgements

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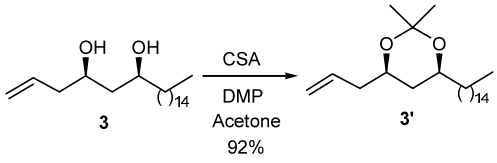
7. *Compound* ***3***: $[\alpha]_D^{20} = -2$ (*c* 1.4, $CHCl_3$); ^{1}H NMR δ: 5.75 (m, 1H), 5.05 (m, 2H), 3.80 (m, 2H), 3.20 (bs, 2H), 2.15 (m, 2H), 1.60–1.20 (m and bs, 30H), 0.80 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR δ: 134.2 (d), 117.9 (t), 72.7 (d), 71.8 (d), 42.4 (t), 42.2 (t), 38.0 (t), 31.8 (t), 29.5 (9t), 29.2 (t), 25.2 (t), 22.5 (t), 13.9 (q).
8. *Acetonide* ***3′***:



   $[\alpha]_D^{20} = -1$ (*c* 1.2, $CHCl_3$); ^{1}H NMR δ: 5.85 (m, 1H), 5.10 (m, 2H), 3.90–3.75 (m, 2H), 2.35–2.11 (m, 2H), 1.55–1.20 (m, 30H), 1.45 (s, 3H), 1.40 (s, 3H), 0.90 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR δ: 134.2 (d), 116.8 (t), 98.2 (s), 68.8 (d), 68.6 (d), 40.7(t), 36.3–31.8–29.6–29.5–29.4–29.2–24.8–22.5 (15t), 30.1 (q), 19.6 (q), 13.9 (q)
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10. *Compound* ***6***: $[\alpha]_D^{20} = -7$ (*c* 1.67, $CHCl_3$); ^{1}H NMR δ: 5.80 (m, 1H), 5.05 (m, 2H), 3.85–3.70 (m, 3H), 2.30–2.10 (m, 2H), 1.60 (m, 4H), 1.25 (bs, 28H), 0.88 (s, 9H), 0.85 (t, $J = 7.0$ Hz, 3H), 0.84 (s, 9H), 0.82 (s, 9H), 0.03 (s, 6H), 0.01 (s, 6H), 0.00 (s, 6H); ^{13}C NMR δ: 134.9 (d), 116.7 (t), 69.4 (2d), 67.4 (d), 45.9 (t), 45.7 (t), 42.0 (t), 36.4 (t), 31.8 (t), 29.7–29.6–29.5–29.4–29.2 (10t), 25.8 (6q), 25.6 (3q), 25.0 (t) 22.5 (t), 17.9 (3s), 13.9 (q), −3.1 (q), −3.9 (q), −4.2 (q), −4.3 (q), −4.4 (q), −4.6 (q).
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13. *Spectroscopic data for compound* ***P1***: ^{1}H NMR (300 MHz) δ: 6.90 (td apparent, $J = 9.9$ and 4.5 Hz, 1H), 6.00 (dt, $J = 1.5$ and 9.9 Hz, 1H), 4.70 (m, 1H), 4.40 (brs, OH, 1H), 4.20 (m, 2H), 3.90 (m, 1H), 3.65 (brs, OH, 1H), 2.44 (m, 2H), 2.10 (m, 1H), 1.85–1.30 (m, 10H), 1.30–1.20 (brs, 24H), 0.88 (t, $J = 7$ Hz, 3H); ^{13}C NMR (400 MHz) δ: 164.2 (s), 145.4 (d), 121.2 (d), 76.7 (d), 73.4 (d), 70.5 (d), 66.0 (d), 43.0 (t), 42.5 (t), 41.9 (t), 38.4 (t), 31.9–29.7–29.6–29.4–25.3–22.7 (14t), 14.1 (q).
14. *Spectroscopic data for compound* ***P2***: ^{1}H NMR (300 MHz) δ: 6.90 (ddd, $J = 9.9$, 5.1 and 3.3 Hz, 1H), 6.00 (dt, $J = 1.5$ and 9.9 Hz, 1H), 4.75 (m, 1H), 4.30 (m, 1H+OH), 4.24 (m, 1H), 3.88 (m, 1H+OH), 3.10 (brs, OH), 2.38 (m, 2H), 1.92–1.40 (m, 10H), 1.30–1.20 (brs, 24H), 0.85 (t, $J = 7$ Hz, 3H); ^{13}C NMR (400 MHz) δ: 165.2 (s), 146.0 (d), 121.6 (d), 75.5 (d), 73.6 (d), 70.9 (d), 64.6 (d), 43.8 (t), 43.0 (t), 42.9 (t), 38.7 (t), 32.3–30.3–30.1–30.0–29.7–25.7–23.0 (14t), 14.5 (q).