Tetrahedron Letters 49 (2008) 4476–4478

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Asymmetric synthesis of (+)-passifloricin A and its 6-epimer

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ARTICLE INFO

Article history:
Received 11 April 2008
Revised 3 May 2008
Accepted 13 May 2008
Available online 16 May 2008

Keywords:
Jacobsen epoxidation
Grubbs' metathesis
Evans' intramolecular oxa-Michael reaction
Maruoka allylation

ABSTRACT

Stereoselective total syntheses of the antiprotozoal natural product (+)-passifloricin A and its C-6 epimer have been achieved in ~5% overall yield. The strategy is based on Jacobsen epoxidation, Grubbs' metathesis and an Evans' intramolecular oxa-Michael reaction.

The δ-lactone ring is an important structural feature of a number of natural products.[1] A few of these natural products also possess a non-polar lipophilic tail, which gives these compounds amphiphilic character. Passifloricin A (Fig. 1, **1a**) is one such natural product isolated from *Passiflora foetida*.[2] This compound has shown interesting antiprotozoal, antifungal properties[3] and has attracted the attention of both analytical and synthetic chemists owing to the ambiguous assignment of the structure.[4] However, Murga et al. synthesized several isomers of this natural product and unequivocally assigned the structure as shown in Figure 1.[4f]

Having a general interest in the total synthesis of bioactive compounds and in particular, six-membered oxygen heterocycles,[5] we have recently employed the intramolecular oxa-Michael reaction[5c–e] of Evans et al. and Grubbs' olefin metathesis[5a] to construct oxygen heterocycles. The retrosynthetic analysis of **1a**/**1b** based on this strategy is shown below in Scheme 1.

Our approach also demonstrates the power of Jacobsen's asymmetric epoxidation[6] as a tool for generating the first stereogenic center at C-13 followed by Sharpless asymmetric epoxidation chemistry to install the next stereogenic carbon at C-10. An intramolecular oxa-Michael reaction allowed exclusive *syn*-installation of the third asymmetric carbon at C-8. Herein, we report our efforts on the total synthesis of passifloricin A (**1a**) and its 6-epimer **1b** (Scheme 2).

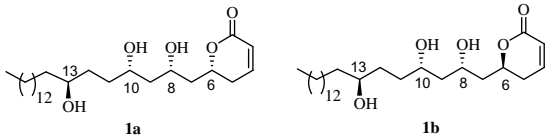
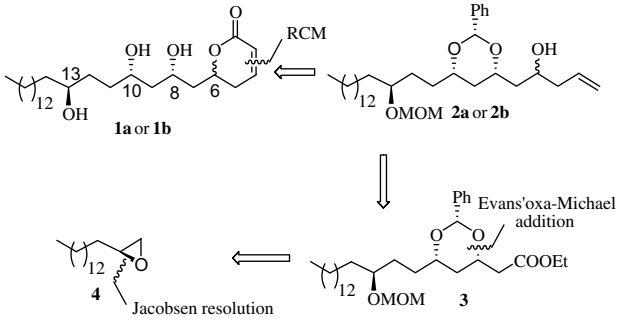


Figure 1. Structure of (+)-passifloricin A (**1a**) and 6-*epi*-passifloricin A (**1b**).



Scheme 1. Retrosynthesis of compounds **1a** and **1b**.

Initially, we investigated the cobalt-based chiral salen complex-mediated resolution of racemic epoxide **4a**, which was obtained in 95% yield from commercially available olefin **5**. The racemic epoxide **4a** was resolved efficiently with Jacobsen's catalyst **A**[6] and the chiral oxirane **4** was obtained in high enantiomeric excess[7] and 45% yield. The regioselective opening of epoxide **4** with allylmagnesium chloride resulted in alcohol **6** in 92% yield. Protection of the alcohol as MOM ether[8] **7** was achieved using MOMCl and diisopropylethylamine which was followed by cross metathesis[9] with ethyl acrylate in the presence of 2 mol % of Grubbs' catalyst **B** (2nd generation) to realize the conjugated ester **8** in quantitative yield. Reduction of the ester functionality in **8** was achieved with DIBAL-H at −15 °C to room temperature to give **9** in 96% isolated

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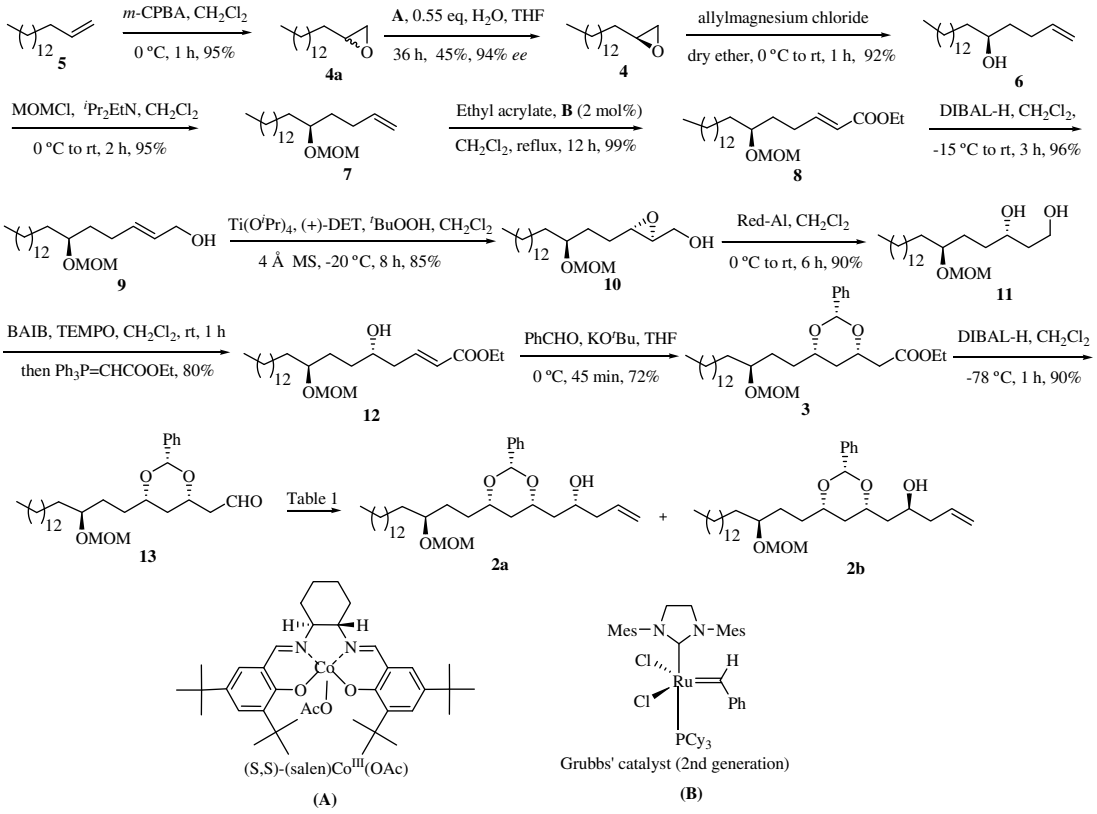
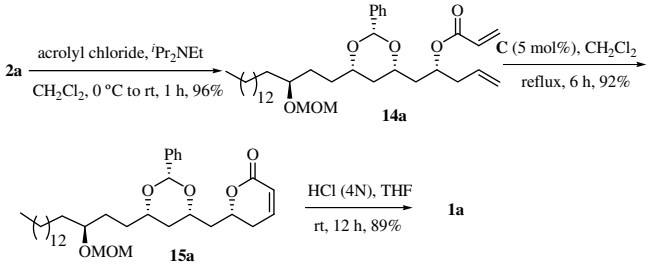
doi:10.1016/j.tetlet.2008.05.070



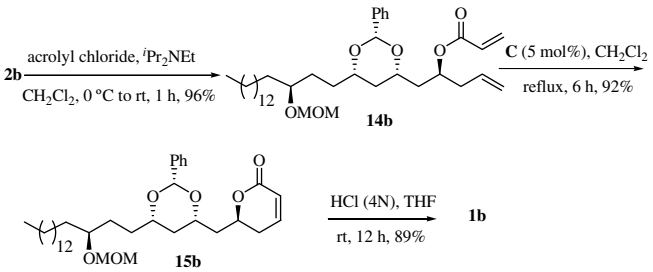
Scheme 2. Stereoselective synthesis of compounds **2a** and **2b**.

yield.[10] The stage was then set for introduction of the following stereogenic hydroxy functionality under Sharpless asymmetric epoxidation conditions[11] using (+)-DET to give chiral epoxy alcohol **10** in 85% isolated yield. The reductive opening of this epoxide was achieved with Red-Al[12] to realize the 1,3-diol **11**. This diol **11**, on selective oxidation in the presence of bis(acetoxy)iodobenzene (BAIB) and 2,2,6,6-tetramethylpiperidine-N-oxide (TEMPO), followed by exposure of the crude β-hydroxy aldehyde to ethoxycarbonylmethylene triphenylphosphorane furnished δ-hydroxy-α,β-unsaturated ester **12** in 80% overall yield for the two steps.[13] This substrate has all the functionalities necessary to perform the tethered Evans' intramolecular oxa-Michael *syn* addition reaction[14] which was executed easily using benzaldehyde and potassium *tert*-butoxide at 0 °C in anhydrous THF to furnish benzylidene acetal **3** in 72% isolated yield. The diastereoselectivity was greater than 95% favoring the more stable *syn*-isomer. The ester group in **3** was reduced to aldehyde[15] **13**, which on allylation gave a diastereomeric mixture of **2a** and **2b** in variable yields and ratios (Table 1).[16] The chiral BINOL-mediated Maruoka allylation[17,5a,e] (Table 1, entry 4) was most efficient providing a *syn*-selectivity of 90% albeit with a low yield of product. Column chromatography allowed us to separate the diastereomers **2a** and **2b**, which were converted independently into (+)-passifloricin A (**1a**) (Scheme 3) and its 6-epimer **1b** (Scheme 3a), respectively.

Diastereomer **2a** was subjected to acrylation with acrolyl chloride in the presence of diisopropylethylamine to generate the diene ester **14a** setting the stage for the Grubbs' ring-closing metathesis



Scheme 3. Stereoselective synthesis of **1a**.



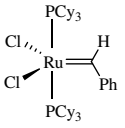
Scheme 3a. Stereoselective synthesis of **1b**.

Table 1
Metal catalyzed allylation of aldehyde **13**

Entry	Reagents and conditions	Yield[a] (%)	*syn*:*anti*[b]
1	Allyl bromide, Mg, dry ether, 0 °C, 1 h	92	55:45
2	Allyl bromide, Zn, THF/satd NH_4Cl, −15 °C, 1 h	98	24:76
3	Allyl bromide, In, THF/H_2O, −15 °C, 1 h	95	32:68
4	Allyltri-*n*-butyltin, Ti(O^iPr)$_4$, $TiCl_4$, Ag_2O, (*R*)-BINOL, CH_2Cl_2, 24 h	45	90:10

[a] Isolated yield after column chromatography purification.
[b] Ratio based on the yields of both isomers after separation by silica gel chromatography.

(RCM)[18] reaction. The diene ester **14a** in CH_2Cl_2 underwent a smooth intramolecular metathesis reaction in the presence of 5 mol % of Grubbs' catalyst **C** (1st generation) to produce the α,β-unsaturated lactone **15a** in 92% yield. Treatment of lactone **15a** with 4 N HCl in THF resulted in cleavage of the MOM-ether and benzylidene acetal to afford passifloricin A (**1a**) in 89% yield.[19] The other diastereomer **2b** was also subjected to the same sequence of reactions to realize the 6-epimer **1b**. The spectroscopic data of both compounds **1a** and **1b** were in full agreement with those reported in the literature.[4f]



Grubbs' Catalyst (1st generation)

(C)

In conclusion, asymmetric total syntheses of (+)-passifloricin A and its 6-epimer have been achieved using Jacobsen's epoxidation, Grubbs' metathesis, an Evans' intramolecular oxa-Michael and a Maruoka allylation as key steps.[20]

Acknowledgment

C.R. and A.S.P. thank CSIR-New Delhi for the award of research fellowships.

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20. *Spectral data of selected compounds*: *(2S)-2-Tetradecyloxirane* (**4**): $[\alpha]_D$ +0.6 (*c* 1.0, $CHCl_3$); IR (KBr): ν_{max} 2925, 2854, 1462, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.86–2.80 (m, 1H); 2.68 (dd, *J* = 5.2, 3.7 Hz, 1H); 2.40 (dd, *J* = 5.2, 2.2 Hz, 1H); 1.54–1.41 (m, 2H); 1.36–1.22 (m, 24H); 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.3, 47.0, 32.5, 31.9, 29.7, 29.6 (several overlapped peaks), 29.4, 25.9, 22.7, 14.1; MS (LC): *m/z* 241.2 $(M+H)^+$; HRMS calcd for $C_{16}H_{32}ONa$ $(M+Na)^+$: 263.2345; found, 263.2350.
Ethyl (2E,6S)-6-(methoxymethyl)-2-icosenoate (**8**): $[\alpha]_D$ +8.7 (*c* 1.0, $CHCl_3$); IR (KBr): ν_{max} 2925, 2853, 1723, 1039 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.93–6.78 (m, 1H); 5.72 (d, *J* = 15.6 Hz, 1H); 4.55–4.47 (m, 2H); 4.08 (q, *J* = 7.0 Hz, 2H); 3.49–3.37 (m, 1H); 3.26 (s, 3H); 2.25–2.12 (m, 2H); 1.60–1.14 (m, 31H); 0.80 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 148.8, 121.4, 95.5, 76.9, 60.0, 55.5, 34.2, 32.6, 31.8, 29.7, 29.6 (several overlapped peaks), 27.9, 25.1, 22.6, 14.2, 14.0; MS (LC): *m/z* 421.2 $(M+Na)^+$; HRMS calcd for $C_{24}H_{46}O_4Na$ $(M+Na)^+$: 421.3293; found, 421.3282.
Ethyl 2-{(2S,4R,6R)-6-[(3S)-3-(methoxymethoxy)heptadecyl]-2-phenyl-1,3-dioxan-4-yl}acetate (**3**): $[\alpha]_D$ +4.5 (*c* 1.0, $CHCl_3$); IR (KBr): ν_{max} 2926, 2853, 1738, 1459, 1031, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46–7.43 (m, 2H); 7.35–7.27 (m, 3H); 5.52 (s, 1H); 4.61 (s, 2H); 4.31–4.20 (m, 1H); 4.15 (q, *J* = 7.5 Hz, 2H); 3.85–3.77 (m, 1H); 3.58–3.49 (m, 1H); 3.35 (m, 3H); 2.70 (dd, *J* = 15.4, 6.7 Hz, 1H); 2.42 (dd, *J* = 15.4, 6.4 Hz, 1H); 1.74–1.19 (m, 35H); 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 138.4, 128.4, 128.0, 125.9, 100.4, 95.3. 77.2, 76.7, 73.1, 60.4, 55.4, 40.9, 36.5, 34.3, 31.8,31.6, 29.7, 29.6 (several overlapped peaks), 29.2, 25.1, 22.6, 14.1, 14.0; MS (LC): *m/z* 571.4 $(M+Na)^+$; HRMS calcd for $C_{33}H_{56}O_6Na$ $(M+Na)^+$: 571.3974; found,571.3969.