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A New Concise Synthesis of (+)-Ipomeamarone, (-)-Ngaione and their stereoisomers

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A new concise and enantio-controlled total synthesis of (+)-ipomeamarone (**1**), a well-known phytoalexin, is described. The key step involved a tetrahydrofuran ring construction from optically active furyl alcohol **5** via π -allyl palladium complex with chiral phosphine ligand. This procedure was also applicable to a synthesis of (-)-ngaione (**2**) and its stereoisomers.

(+)-Ipomeamarone (**1**) is a well-known furanosesquiterpene as one of the first isolated phytoalexins from mold-damaged sweet potatoes *Ipomea batatas* by Hiura¹ and its structure was elucidated by Kubota and Matsuura in 1953.² Absolute stereochemistry of **1** was determined as (2*S*, 5*R*) by Nakanishi in 1983.³ Its stereoisomers, (-)-ngaione (**2**) and (+)-epingaione (**3**), are also known as toxic constituents isolated from *Myoporium deserti*.⁴ These compounds contain the 2,5-disubstituted tetrahydrofuran skeleton, which were found in many naturally occurring antibiotics of monensin type. The unique structure as well as significant biological activities for the toxicological studies led to us to undertake a new enantioselective synthesis of **1**. Despite three asymmetric total syntheses of **1** have been already published,⁵ we believed a shorter and concise access was possible. Specifically, our goal was to develop a synthetic strategy to prepare **1** and its stereoisomers in a straightforward manner for further biological evaluations. Herein we like to report a new concise and enantio-controlled total synthesis of (+)-ipomeamarone (**1**) and its stereoisomers.

Figure 1. Structures of (+)-ipomeamarone (**1**), (-)-ngaione (**2**) and (-)-epingaione (**3**).

Our synthetic strategy of **1**, outlined in Scheme 1, involves THF ring construction from optically active furyl alcohol **5** via π -allyl palladium complex with chiral phosphine ligand. Furyl alcohol **5** was to be synthesized via CBS reduction of **6**, which was obtained by Stille coupling of **7** and **9**.

Our total synthesis of **1** commenced with geranyl acetate (Scheme 2). Selective epoxidation on the terminal double bond with *m*CPBA followed by oxidation with HIO₄ afforded aldehyde **11** in 67% yield for 2 steps.⁶ Jones oxidation of **11** gave acid **8** in 74% yield. Following treatment of **8** with oxalyl chloride in the presence of DMF (catalytic amount) led to acid chloride **7**, which was used directly for Stille coupling reaction without further purifications.

Scheme 2. Preparation of furyl ketone **6**

Metallation of 3-bromofuran⁷ using *n*-butyl lithium proceeded smoothly to afford **9** by the addition of tributyltin chloride. The cross-coupling reaction of **9** and acid chloride **7**

was carried out using 5 mol % of $\text{PdCl}_2(\text{PPh}_3)_2$ in benzene to afford **6** in 67% yield.

The Stille coupling product **6** was subjected to enantioselective reduction using the CBS catalyst and borane, yielding furyl alcohol **5** with high enantiomeric excess (>95% ee) in 89% yield.

The absolute configuration of **5** was confirmed by advanced Mosher ester analysis (Figure 2),⁸ which revealed that reduction using (*S*)-(-)-2-methyloxazaborolidine resulted in the formation of the *R* alcohol. This result is in agreement with the expected transition state for the CBS reduction.⁹

Few examples of stereoselective allylic *O*-alkylations at tertiary centers with aliphatic alcohols.¹⁰ We anticipated that the inherent diastereofacial preference of **5** would be to form **4b** (*trans*) rather than the desired *cis* product **4a**.¹¹ Initially, we examined Pd-catalyzed cyclization of **5** with achiral phosphine ligands (Table 1).

Table 1. Pd-catalyzed cyclization of **5** with achiral ligands

$\xrightarrow[\text{reflux, 24h}]{\text{Pd}_2\text{dba}_3 (5 \text{ mol\%}) \text{ Phosphine ligand THF}}$			
Entry	Phosphine ligand	4a:4b^a	Conv. ^a
1	PPh_3 (40 mol%)	No reaction	-
2	$\text{P}(o\text{-tolyl})_3$ (40 mol%)	No reaction	-
3	DPPE (20 mol%)	1:1.2	9%
4	DPPP (20 mol%)	1:1.3	9%
5	DPPB (20 mol%)	1:1.7	96%

^a Determined by GC analysis (DB-5 column).¹²

With mono-phosphine, the desired reaction would not proceed at all (Entries 1 and 2), whereas 20 mol% of DPPB accelerated the desired reaction in 96% conversion (Entry 5). These results suggested us a C4 bridged diphosphine ligand is crucial to proceed the cyclization smoothly.

Then we screened a range of chiral catalysts to figure out that Pd_2dba_3 with (*R*)-SegPhos¹³ enabled us to overcome the substrate's diastereofacial bias and favor **4a** (Table 2, entry 3). Matching/mismatching effects were observed here; (*S*)-SegPhos gave substantial (1:4.2) selectivity for the *trans* product **4b** (Entry 4).

Table 2. Pd-catalyzed cyclization of **5** with chiral ligands

$\xrightarrow[\text{reflux, 24h}]{\text{Pd}_2\text{dba}_3 (5 \text{ mol\%}) \text{ Chiral Phosphine ligand THF}}$			
Entry	Chiral Phosphine ligand (20 mol%)	4a:4b^a	Conv. ^a
1	(<i>R</i>)-BINAP	1.2:1	94%
2	(<i>R</i>)-C ₃ TunePhos	2.1:1	98%
3	(<i>R</i>)-SegPhos	3.7:1	98%
4	(<i>S</i>)-SegPhos	1:4.2	95%

^a Determined by GC analysis (DB-5 column).¹²

The structure of **4a** (*cis*) and **4b** (*trans*) were confirmed by subsequent nOe experiments (signal enhancements are indicated by arrows in Figure 3).

4a was subjected to hydroboration with $\text{BH}_3\cdot\text{THF}$ and the corresponding alcohol **12** was obtained with 77% (Scheme 4). Dess–Martin oxidation of alcohol **12** provides the known aldehyde (2*S*, 5*R*)-**13** in 96% yield, whose analytical and spectral data were in good agreement with the literature report.^{5c,14}

To complete the synthesis of **1**, the previously reported endgame^{5c} has been slightly modified. The Grignard addition of isobutylmagnesium bromide to (2*S*, 5*R*)-**13** gave alcohol **14** as a 1:1 mixture of diastereomers quantitatively, which were re-oxidized with Dess–Martin periodinane to afford the desired (+)-ipomeamarone (**1**) with the correct stereochemistry in 95% yield. The spectral data of our synthetic (+)-ipomeamarone agree satisfactorily with those reported.^{3,15} A new total synthesis of (+)-ipomeamarone (**1**) has been thus achieved in 10 steps with 15.9% overall yield.

Pd-catalyzed cyclization of *ent*-**5**, obtained by reduction of **6** with (*R*)-Me-CBS catalyst, provided *ent*-**4a** (with (*R*)-SegPhos) and *ent*-**4b** (with (*S*)-SegPhos), respectively. The same procedure above mentioned are applicable to *ent*-**4a**,

ent-4b and **4b**, which were converted to (2*R*, 5*S*)-**13**, (2*S*, 5*S*)-**13** and (2*R*, 5*R*)-**13**, respectively.¹⁶

Figure 3. Structures of **ent-4a**, **ent-4b** and the other stereoisomers **13**

In summary, (+)-ipomeamarone, (–)-ngaione and their stereoisomers have been synthesized from the commercially available geranyl acetate, involving a Pd-catalyzed cyclization with (*R*)- or (*S*)-SegPhos as a key step to furnish the THF ring skeleton.

This paper is dedicated to the memory of the late emeritus Professor Takashi Tokoroyama at Osaka City University.

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- 16 (2*R*, 5*S*)-**13**: colorless liquid, $[\alpha]_D^{-14.4^\circ}$ (c 1.7, MeOH); ¹H NMR (400 MHz, CDCl₃) δ 9.83 (t, *J* = 2.7 Hz, 1H), 7.38–7.36 (m, 2H), 6.34 (m, 1H), 4.98 (t, *J* = 7.1 Hz, 1H), 2.62 (d, *J* = 2.7 Hz, 2H), 2.30 (m, 1H), 2.05–1.92 (m, 3H), 1.39 (s, 3H); ¹³C NMR (100 MHz,

CDCl₃) δ 202.1, 143.4, 139.1, 126.9, 108.6, 87.1, 73.2, 54.9, 37.8, 33.2, 27.2; HRMS(EI) *m/z*: [M]⁺ calcd for C₁₁H₁₄O₃ 194.0943, found 194.0934. (2*S*, 5*S*)-**13**: colorless liquid, $[\alpha]_D^{-13.8^\circ}$ (c 1.1, MeOH); ¹H NMR (400 MHz, CDCl₃) δ 9.86 (t, *J* = 2.7 Hz, 1H), 7.38 (m, 2H), 6.38 (m, 1H), 4.97 (t, *J* = 7.1 Hz, 1H), 2.66 (d, *J* = 2.7 Hz, 2H), 2.27 (m, 1H), 2.02–1.91 (m, 3H), 1.41 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 202.1, 143.4, 139.3, 127.1, 108.6, 81.1, 73.9, 54.3, 38.0, 33.3, 28.1; HRMS(EI) *m/z*: [M]⁺ calcd for C₁₁H₁₄O₃ 194.0943, found 194.0936. (2*R*, 5*R*)-**13**: colorless liquid, $[\alpha]_D^{+15.5^\circ}$ (c 1.0, MeOH); ¹H NMR (400 MHz, CDCl₃) δ 9.86 (t, *J* = 2.7 Hz, 1H), 7.38 (m, 2H), 6.38 (m, 1H), 4.97 (t, *J* = 7.1 Hz, 1H), 2.66 (d, *J* = 2.7 Hz, 2H), 2.27 (m, 1H), 2.02–1.91 (m, 3H), 1.41 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 202.1, 143.4, 139.3, 127.1, 108.6, 81.1, 73.9, 54.3, 38.0, 33.3, 28.1; HRMS(EI) *m/z*: [M]⁺ calcd for C₁₁H₁₄O₃ 194.0943, found 194.0941

Graphical Abstract

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A brief abstract

A new concise and enantio-controlled formal total synthesis of (+)-ipomeamarone (**1**), a well-known phytoalexin, is described. The key step involved a tetrahydrofuran ring construction from optically active furyl alcohol **5** via π -allyl palladium complex with chiral phosphine ligand. This procedure was also applicable to a synthesis of (–)-ngaione (**2**) and its stereoisomers.

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