

# A concise and straightforward approach to total synthesis of (+)-Strictifolione and formal synthesis of Cryptofolione via a unified strategy

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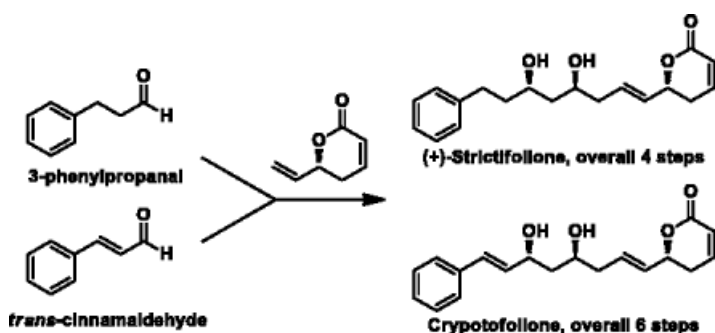
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## ABSTRACT

We describe a concise and straightforward approach to the total syntheses of (+)-Strictifolione and Cryptofolione in the longest linear sequences of four steps and six steps from 3-phenyl propanal and trans-cinnamaldehyde, respectively. The route utilized a titanium tetraisopropoxide/(R)-[1,1'-binaphthalene]-2,2'-diol catalyzed Mukaiyama aldol reaction, indium(0)-promoted Barbier reaction, and olefin cross-metathesis as the key reactions.

## GRAPHICAL ABSTRACT



**KEYWORDS** Strictifolione; Cryptofolione; total synthesis; Barbier reaction; olefin cross-metathesis

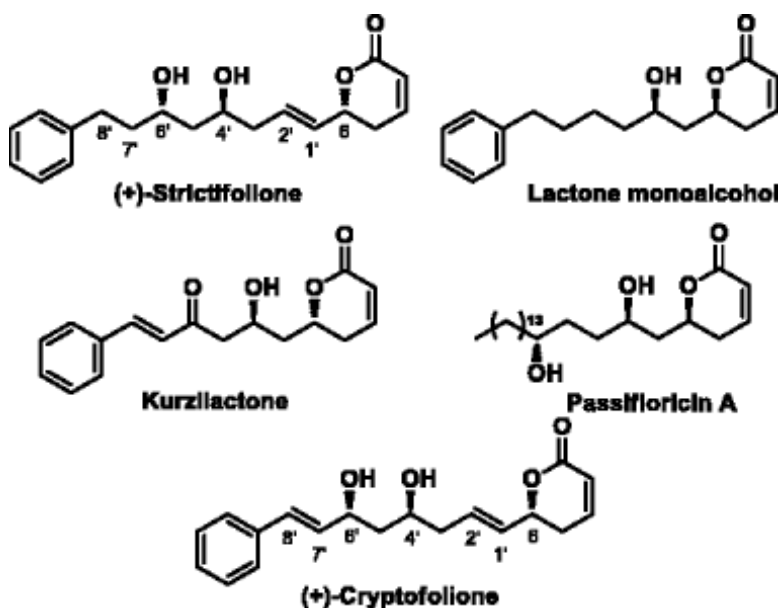
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## Introduction

The potential Michael acceptor,  $\alpha,\beta$ -unsaturated  $\delta$ -lactone (also named 5,6-dihydro- $\alpha$ -pyrone) is found in many natural products possessing useful pharmacological properties, such as anti-inflammatory, antiproliferative and anticancer activity.<sup>[1]</sup> The related natural products include Strictifolione, Cryptofolione, Lactone monoalcohol,<sup>[2]</sup> Kurzilactone,<sup>[3]</sup> Passifloricin A,<sup>[4]</sup> Tarchonanthuslactone<sup>[5]</sup> (Figure 1). (+)-Strictifolione was isolated by Aimi et al. from the stem bark of *Cryptocarya strictifolia* which is indigenous to the Indonesian tropical rainforest.<sup>[6]</sup> The relative stereochemistry of Strictifolione's structure was elucidated based on the spectroscopic method and the absolute configuration of the three chiral centers was established by Aimi's group in 2002 through its first total synthesis.<sup>[7a]</sup> Cryptofolione was isolated from *Cryptocarya latifolia*, *C. myrtifolia* and *C. alba*<sup>[8]</sup> and its structure was determined through an asymmetric total synthesis in 2005.<sup>[9a]</sup> Cryptofolione showed interesting bioactivity, such as reducing the number of *Trypanosoma cruzi* trypanosomastigotes by 77% at 250  $\mu\text{g/mL}$ , demonstrating cytotoxicity in both macrophages and *T. cruzi* amastigotes, and displaying inhibitory effects on the promastigote form of *Leishmania* species amongst others.<sup>[10]</sup>

Figure 1. Example of natural products possessing  $\alpha,\beta$ -unsaturated  $\delta$ -lactone.



As two typical members of this class of natural products containing an  $\alpha,\beta$ -unsaturated  $\delta$ -lactone moiety, *syn*- or *anti*-1,3-diol or 1,3,5-triol and a lipophilic subunit, (+)-Strictifolione and Cryptofolione attracted considerable interests in their total syntheses. Over the past decade, many efforts have been made towards the total syntheses of Stric-

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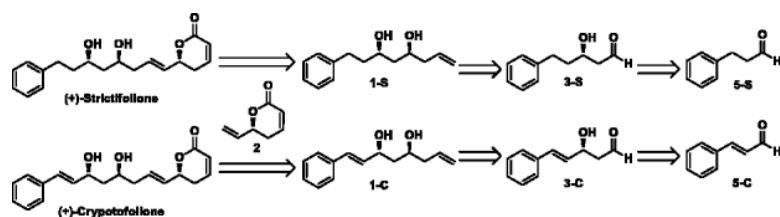
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folione<sup>[7]</sup> and Cryptofolione<sup>[9]</sup>. Strictifolione has almost the same structure as Cryptofolione except for the saturated bond at C7'-C8'; both have a 1,3-*anti* diol unit connecting the C-6 substituent of the  $\alpha,\beta$ -unsaturated  $\delta$ -lactone moiety with a double bond. Most of the published synthetic routes for Strictifolione and Cryptofolione involved scission of the unsaturated bond at C1'-C2' utilizing a convergent strategy. For the construction of stereogenic centers, many and varied protocols were employed, such as chiral pool syntheses,<sup>[7e]</sup> enantioselective allyltitanation,<sup>[7b]</sup> enzymatic reduction,<sup>[7j]</sup> asymmetric acetate aldol reaction<sup>[9f]</sup> and so on. Curiously, there is no synthetic report of these two molecules using a unified synthetic strategy. The shortest approach was explored by Hanson, who recently applied a three-pot process to accomplish a modular approach toward (+)-Strictifolione and the related natural products.<sup>[7k]</sup> As a part of our research aimed at developing a concise synthesis of natural products possessing an  $\alpha,\beta$ -unsaturated  $\delta$ -lactone,<sup>[11]</sup> we decided to devise a unified, concise and efficient route to (+)-Strictifolione and Cryptofolione. It appears that the key to a shorter total synthesis is fewer synthetic steps towards the fragments. Therefore, here we describe a concise and practical total synthesis of (+)-Strictifolione and Cryptofolione through rapid preparation of two fragments.

## Results and discussion

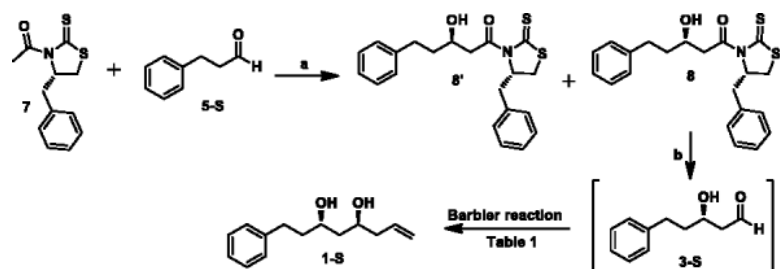
Our retrosynthetic analysis is shown in Scheme 1. (+)-Strictifolione and Cryptofolione were disconnected into two similar fragments, **1-S/1-C** and **2**, via a cross-metathesis reaction. For the fragment **1-S/1-C**, the 1,3-*anti*-diol was assumed to be obtained via an In (0) promoted Barbier allylation from aldehyde **3-S/3-C**,<sup>[12]</sup> which would be readily prepared from aldehyde **5-S/5-C** using a Crimmins modified Evans aldol reaction.<sup>[13]</sup> Another known building block **2**<sup>[7f,h,j]</sup>, was devised to be readily prepared from  $\delta$ -hydroxyl  $\beta$ -keto ester **4**, in which the chiral hydroxyl might be achieved employing an asymmetric Muakiyama aldol reaction.<sup>[9e,14]</sup>

Scheme 1. Retrosynthetic analysis of Strictifolione and Cryptofolione.



As shown in Scheme 2, we began our synthesis of (+)-Strictifolione with the preparation of fragment **1-S**, using commercially available 3-phenyl propanol **5-S**. 3-phenyl propanol was subjected to a Crimmins modified Evans aldol reaction when treated with compound **7** in the presence of  $\text{TiCl}_4$  and DIPEA to give **8** in a yield of 84% (dr = 2.5:1). Alcohol **8** then needed to be reduced to  $\beta$ -hydroxyl aldehyde **3-S**. The presumed instability of **3-S** was evident, so the crude **3-S** was immediately subjected to the subsequent Barbier reaction.

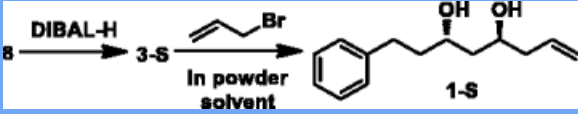
Scheme 2. Synthetic route of intermediate **1-S**. Reagents and conditions: (a)  $\text{TiCl}_4$ , DIPEA,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 84% (d.r. = 2.5:1); (b) DIBAL-H,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ .



Following Li's protocol,<sup>[12a]</sup> we first attempted the allylation in water, however, we only obtained the 1,3-diol **1-S** in 60% after 72 h with no diastereoselectivity (entry 1 in Table 1). This disappointing ratio impelled us to optimize

this transformation. As shown in Table 1, by simply adjusting the ratio of solvent (water to THF), we found the desired **1-S** was obtained in 55% over two steps with the dr ratio of 6:1 (*anti*:*syn*) when using THF/H<sub>2</sub>O (1:1) as the solvent mixture (entry 2). However, increasing the ratio of THF only resulted in poor diastereoselectivity (entry 3) and yield (entry 4).

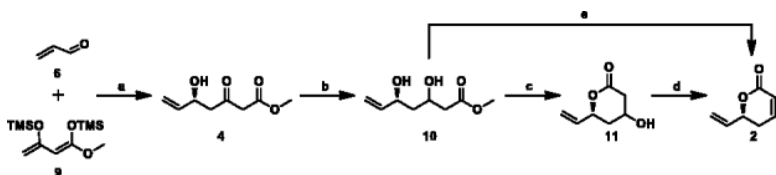
Table 1. Optimization of Barbier reaction. Table Layout

				
Entry	Solvent	Time (h)	<i>Anti</i> : <i>syn</i> <sup>a</sup>	Yield (%) <sup>b</sup>
1	H <sub>2</sub> O	72	1:1	60
2	THF/H <sub>2</sub> O (1:1)	72	6:1	55
3	THF/H <sub>2</sub> O (10:1)	72	3:1	50
4	THF	72	–	Trace

<sup>a</sup> dr value was determined by NMR spectra.  
<sup>b</sup> Combined yield based on isolation by column chromatography from compound **8**.

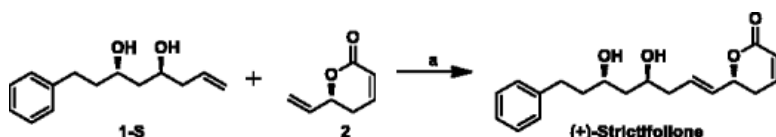
Synthesis of fragment **2** started from acrylaldehyde **6**. Retrosynthetically, the chiral hydroxyl was installed through Mukaiyama aldol reaction. Thus, the addition of acrylaldehyde **6** to Chan's diene in the presence of Ti(O<sup>i</sup>Pr)<sub>4</sub>/(*R*)-BINOL and molecular sieves in THF at –78 °C afforded  $\delta$ -hydroxyl  $\beta$ -keto ester **4** smoothly in 83% yield with 96% ee value (Scheme 3). Considering the requirement for a  $\beta$ -hydroxyl, the intermediate **4** was then subjected to reduction with NaBH<sub>4</sub> to furnish diol **10** in 85% without determination of dr value. Cyclization of **10** with PPTS in refluxing benzene smoothly afforded lactone **11** in a yield of 95%. The compound **11** was subsequently treated with MsCl and triethylamine in DCM at 0 °C to give fragment **2** via a one-pot process in 80% yield. At higher temperature, the desired fragment **2** was able to be prepared from **10** directly.<sup>[15]</sup> Thus, lactone **2** was obtained from diol **10** in 90% by refluxing in toluene (Scheme 3) [AQ3].

Scheme 3. Synthesis of intermediate **2**. Reagents and conditions: (a) Ti(O<sup>i</sup>Pr)<sub>4</sub>, (*R*)-BINOL, THF, –78 °C, 83%, 96% ee; (b) NaBH<sub>4</sub>, MeOH, 0 °C, 85%; (c) PPTS, benzene, reflux, 95%; (d) MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 80%; (e) PPTS, toluene, reflux, 90%.



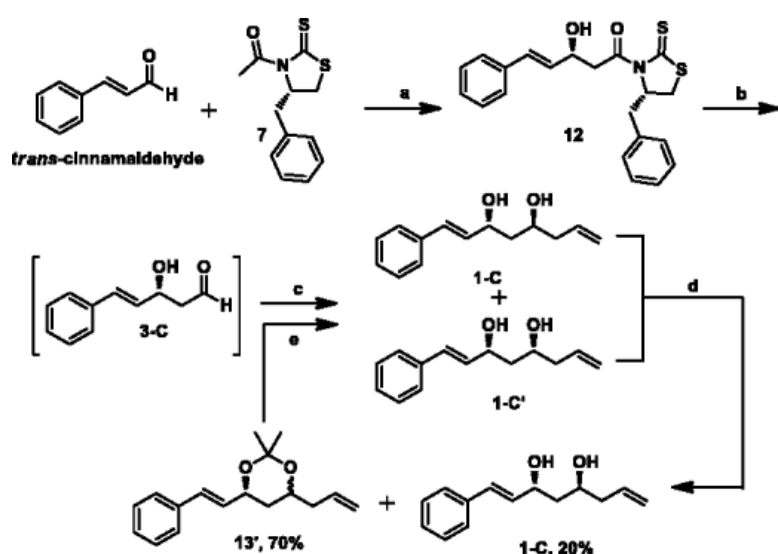
With fragment **1-S** and **2** in hand, we conducted the cross-metathesis coupling of two fragments. Following the known procedure,<sup>[7]</sup> the olefin cross-metathesis reaction of **1-S** and **2** in the presence of Grubbs' second generation catalyst furnished (+)-Strictifollone (Scheme 4).

Scheme 4. Synthesis of (+)-Strictifollone. Reagents and conditions: (a) Grubbs' 2nd CH<sub>2</sub>Cl<sub>2</sub>, 50 °C, 80%.



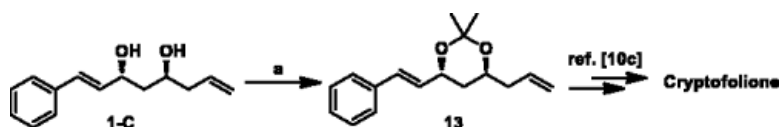
The same synthetic sequence described above was applied to Cryptofolione by replacing 3-phenyl propanol with *trans*-cinnamaldehyde. As depicted in Scheme 5, Crimmins modified Evans aldol reaction of cinnamaldehyde and compound **7** easily gave alcohol **12** following Yadav's procedure.<sup>[9f]</sup> The prepared **12** was subjected to a DIBAL-H reduction to prepare aldehyde **3-C**, and then, without purification, the crude of aldehyde **3-C** was subjected to the In (0)-promoted Barbier reaction in THF/H<sub>2</sub>O (10:1) to afford *anti*-diol **1-C** in 75% yield over two steps with moderate diastereoselectivity (dr = 4:1). **1-C** was too difficult to be separated efficiently from its diastereoisomer. However, when they were subjected to protection with 2,2-dimethoxypropane, **1-C** would be obtained in 20% accompanied by the protected diol mixtures **13'**. **13'** were then treated with 4 N HCl gave the free diols, which then performed the above kinetic resolution. After three kinetic resolutions, we could obtain about one half of **1-C** (48%) from the mixture of the diastereoisomers.

Scheme 5. Synthetic route of intermediate **1-C**. Reagents and conditions: (a) see ref. <sup>[9f]</sup>; (b) DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>; (c) In powder, 3-bromoprop-1-ene, THF: H<sub>2</sub>O = 1:1, 75% (d.r. = 4:1) over two steps; (d) p-TsOH, CH<sub>2</sub>Cl<sub>2</sub>, 2,2-dimethoxypropane, 0 °C, 5.5 h; (e) 4N HCl, MeCN, 0 °C, 93%.



An attempt to conduct the cross-metathesis reaction of compound **1-C** with fragment **2** failed, therefore, the hydroxyls of **1-C** were subsequently protected with 2,2-dimethoxypropane to give the intermediate **13**, previously reported as a fragment, which was coupled with lactone **2** to easily furnish Cryptofolione via a CM reaction (Scheme 6).<sup>[9c]</sup> The physical and spectral data (<sup>1</sup>H, <sup>13</sup>C) of compound **13** from our lab were in agreement with those reported in the literature (Scheme 6).

Scheme 6. Formal synthesis of Cryptofolione. Reagents and conditions: (a) p-TsOH, CH<sub>2</sub>Cl<sub>2</sub>, 2,2-dimethoxy-propane, 0 °C, overnight, 83%.



## Conclusion

Thus, we have successfully achieved the total synthesis of (+)-Strictifolione and formal synthesis of Cryptofolione via a unified strategy. To the best of our knowledge, the present synthetic route represents the shortest route to these two molecules. We separated the target into two fragments, and the linear route was only 4 steps and 6 steps for (+)-

Strictifolione and Cryptofolione respectively. This synthetic approach provides an alternative route to these natural products of similar structure.

## Experimental

All air and water sensitive reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions unless otherwise noted. All the chemicals were purchased commercially and used without further purification. Anhydrous THF and was distilled from sodium-benzophenone, toluene was distilled from sodium, and dichloromethane was distilled from calcium hydride. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (60F-254) that were analyzed by staining with  $\text{KMnO}_4$  (200 mL  $\text{H}_2\text{O}$  of 1.5 g  $\text{KMnO}_4$ , 10 g  $\text{K}_2\text{CO}_3$  and 1.25 mL of 10% aqueous  $\text{NaOH}$ ), fluorescence upon 254 nm irradiation or by staining with anisaldehyde (450 mL of 95%  $\text{EtOH}$ , 25 mL of conc.  $\text{H}_2\text{SO}_4$ , 15 mL of acetic acid, and 25 mL of anisaldehyde). Silica gel (60, particle size 0.040–0.063 mm) was used for flash chromatography. IR spectra were obtained using FT-IR Spectrometer. NMR spectra were recorded on either a 300 ( $^1\text{H}$ : 300 MHz,  $^{13}\text{C}$ : 75 MHz), 400 ( $^1\text{H}$ : 400 MHz,  $^{13}\text{C}$ : 100 MHz), or 500 ( $^1\text{H}$ : 500 MHz,  $^{13}\text{C}$ : 125 MHz). The following abbreviations were used to explain the multiplicities: s: singlet; d: doublet; t: triplet; q: quartet; m: multiplet; b: broad. High-resolution mass spectra were obtained from a MALDI-TOF mass spectrometer.

### (3S,5S)-1-phenyloct-7-ene-3,5-diol (1-S)

To a stirred mixture of **8** (0.2 g, 0.52 mmol) in THF (5 mL) was added DIBAL-H (1.5 mmol, 1.5 mL, 1 M in toluene) dropwise at  $-78^\circ\text{C}$ . After stirring at  $-78^\circ\text{C}$  for 0.5 hour, the reaction was quenched by addition of a saturated potassium sodium tartrate aqueous solution (20 mL), and the aqueous phase was extracted with ethyl acetate (50 mL  $\times$  3). The combined organic extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated and gave a yellow oil as the crude product **3-S**. Without further purification, the crude **3-S** was used in the next reaction.

To a stirred solution of crude **3-S** in THF/ $\text{H}_2\text{O}$  (vol/vol = 1:1, 5 mL) was added Indium powder (72 mg, 0.62 mmol) and allyl bromide (70  $\mu\text{L}$ , 0.75 mmol). The resulting mixture was stirred at room temperature till the aldehyde **3-S** was consumed. Then the reaction was diluted by addition of ethyl acetate (5 mL), and the aqueous phase was extracted with ethyl acetate (5 mL  $\times$  2). The combined organic extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. Silica gel flash column chromatography (hexanes/ethyl acetate = 5:1) of the residue gave a yellow oil (0.063 g, 0.29 mmol, 55% (d.r. = 6:1)) as the product **1-S**.

$[\alpha]_{\text{D}}^{25} = +4.23$  (c = 1.0,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34 – 7.14 (m, 5H), 5.88 – 5.72 (m, 1H), 5.16 (d,  $J = 1.0$  Hz, 1H), 5.14 – 5.09 (m, 1H), 4.06 – 3.92 (m, 2H), 2.73 (dddd,  $J = 34.3, 13.7, 9.6, 6.3$  Hz, 2H), 2.31 – 2.22 (m, 2H), 1.92 – 1.72 (m, 2H), 1.69 – 1.63 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  142.09, 134.61, 128.55, 128.52, 125.99, 118.54, 68.93, 68.37, 42.12, 41.99, 39.15, 32.32; IR: 3347, 1641, 1496, 1454; HRMS:  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{20}\text{NaO}_2$   $[\text{M} + \text{Na}]^+$  243.1356, found 243.1356.

Full experimental detail and  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, HPLC traces can be found via the Supplementary Content section of this article's Web page.

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## COMMENTS

C1 Author: T.x; :

C2 Author: &eacute;; :

C3 Author: Kurzilactone from Cryptocarya kurzii; :

C4 Author: Total Synthesis of (+)-Strictifolione.; :

C5 Author: N; :

C6 Author: Natural product (+)-Strictifolione synthetic method.; :

C7 Author: Asymmetric Synthesis of Cryptofolione and Determination of Its Absolute Configuration.; :

C8 Author: Efficient Stereoselective Total Synthesis of (+)-Cryptofolione and the First Synthesis of (&ndash;)-Cryptocaryalactone.; :

- C9 Author: 26, ; ;  
C10 Author: A Concise and Versatile Total Synthesis of All Stereoisomers of Tarchonanthus lactone.; ;  
C11 Author: . DOI: 10.1016/S0378-8741(00)00183-5.; ;  
C12 Author: DOI: 10.1021/jo101875w.; ;  
C13 Author: . DOI: 10.1016/S0031-9422(99)00532-4.; ;  
C14 Author: &uacute;; ;  
C15 Author: . DOI: 10.1002/pca.818.; ;  
C16 Author: . DOI: 10.1016/j.tet.2004.08.008.; ;  
C17 Author: . DOI: 10.3892/or.6.4.843.; ;