



**Original citation:**

Fang, Zhijia (Researcher in chemistry), Clarkson, Guy J. and Wills, Martin. (2013) Asymmetric reduction of 2,2-dimethyl-6-(2-oxoalkyl/oxoaryl)-1,3-dioxin-4-ones and application to the synthesis of (+)-yashabushitriol. *Tetrahedron Letters*, Volume 54 (Number 50). pp. 6834-6837

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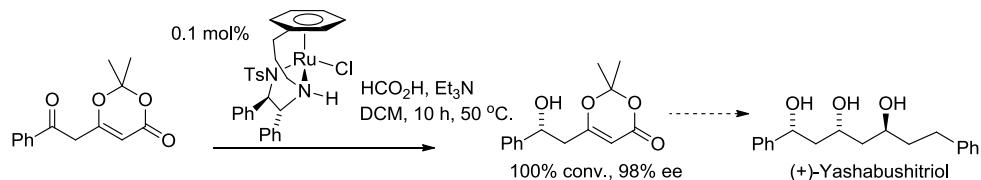
## Graphical Abstract

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**Asymmetric reduction of 2,2-dimethyl-6-(2-oxoalkyl/oxoaryl)-1,3-dioxin-4-ones and application to the total synthesis of (+)-yashabushitriol**

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Zhijia (*Amphi*) Fang, Guy J. Clarkson, Martin Wills.





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# Asymmetric reduction of 2,2-dimethyl-6-(2-oxoalkyl/oxoaryl)-1,3-dioxin-4-ones and application to the synthesis of (+)-yashabushitriol

Zhijia (Amphi) Fang, Guy J. Clarkson, Martin Wills.\*

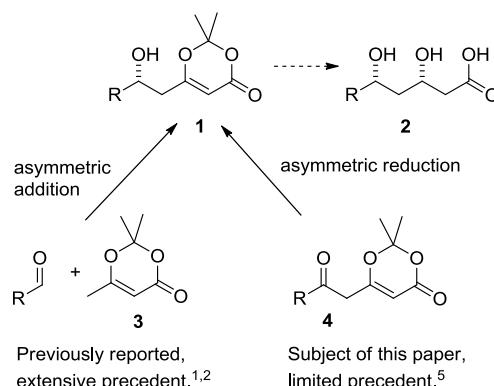
Department of Chemistry, The University of Warwick, Coventry, CV4 7AL, UK.

**Abstract**— The asymmetric transfer hydrogenation of a series of 2,2-dimethyl-6-(2-oxoalkyl)-1,3-dioxin-4-ones and 2,2-dimethyl-6-(2-oxoaryl)-1,3-dioxin-4-ones was achieved in high enantiomeric excess using a Ru(II) catalyst. The aryl substrates were most compatible with the methodology and this process facilitated a total synthesis of enantiomerically pure (+)-yashabushitriol. © 2015 Elsevier Science. All rights reserved

**Keywords:**

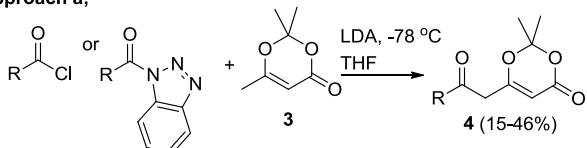
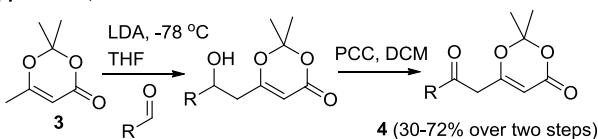
Asymmetric catalysis  
Ketone reduction  
Transfer hydrogenation  
Ruthenium  
2,2-Dimethyl-4-dioxinone  
(+)-Yashabushitriol

The asymmetric synthesis of alcohols of general structure **1**,<sup>1,2</sup> containing a 2,2-dimethyl-1,3-dioxinone structure, represents a valuable approach to the synthesis of a number of important target molecules, notably 3,5-dihydroxy acids **2**<sup>3</sup> which are components of several cholesterol-lowering drugs.<sup>4</sup> A popular approach to these structures has been through the initial addition of dioxinone **3** to an aldehyde under the control of an asymmetric catalyst, leading to formation of **1** in high enantiomeric excess.<sup>2,3</sup> Subsequent hydrolysis of the dioxinone and diastereoselective reduction of the resulting ketone complete the route to general structure **2**. An alternative approach to **1** would be by the asymmetric reduction of ketones of general structure **4**, however this has been less extensively explored.<sup>5</sup> In this paper, we describe a method for the highly enantioselective reduction of ketones of type **4** and the application of this method to the total synthesis of the natural product (+)-yashabushitriol.<sup>6</sup>



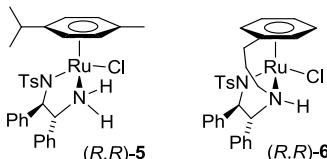
Initially, an approach to the synthesis of ketones **4** was required. Previous methods in the literature fall into two broad groups (Scheme 1); a) addition of the anion from **3** to an appropriate carboxylate reagent such as an acid chloride or acetylbenzotriazole,<sup>7</sup> or b) addition of an anion from **3** to an aldehyde followed by oxidation.<sup>2,8</sup> We first prepared a number of derivatives using the reaction with the lithium enolate of **3** and an acyl donor. Although this worked well in some cases, the yields were generally low. Using approach b, the first step of which has also been employed in an asymmetric sense using a chiral catalyst,<sup>2</sup> several derivatives were prepared in improved overall yields.

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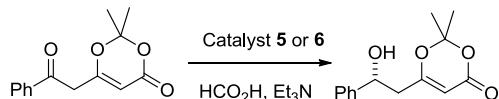
**Approach a;****Approach b;**

**Scheme 1.** Synthetic approaches to reduction substrates in Table 2.

Asymmetric reduction of **4** ( $R=\text{Ph}$ ) was investigated using the known transfer hydrogenation catalysts **(R,R)-5** and **(R,R)-6** (Table 1),<sup>9,10</sup> using formic acid / triethylamine (FA/TEA) as the reducing agent. The addition of solvent was found to be advantageous, with DCM and acetonitrile giving the best results when used with catalyst **5** at an S/C ratio of 50. However the tethered catalyst **6** proved to be the most active, delivering the product in the shortest times. The S/C ratio could be raised to 1000 without loss of conversion or ee, although the reaction times were much longer. However increasing the temperature to 50 °C facilitated full reduction in just 10 hours at an S/C ratio of 1000 without loss of enantioselectivity.



**Table 1.** Reductions of **4** ( $R=\text{Ph}$ ) using catalysts **5** and **6**.<sup>a</sup>



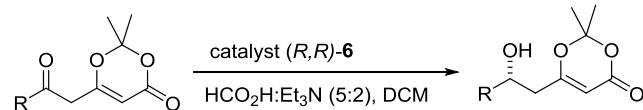
Entr y	Catalyst	Solvent <sup>b</sup>	S/C	T (°C)	Time (h)	Conv (%) <sup>c</sup>	ee (%) <sup>d</sup>
1	<b>(R,R)-5</b>	None	50/1	r.t.	80	<10	-
2	<b>(R,R)-5</b>	EtOAc	50/1	r.t.	80	33	98 (R)
3	<b>(R,R)-5</b>	THF	50/1	r.t.	80	63	98 (R)
4	<b>(R,R)-5</b>	$\text{CH}_2\text{Cl}_2$	50/1	r.t.	13	100	98 (R)
5	<b>(R,R)-5</b>	$\text{CH}_3\text{CN}$	50/1	r.t.	13	100	98 (R)
6	<b>(R,R)-6</b>	$\text{CH}_2\text{Cl}_2$	100/1	r.t.	7	100	98 (R)
7	<b>(R,R)-6</b>	$\text{CH}_2\text{Cl}_2$	500/1	r.t.	29	100	98 (R)
8	<b>(R,R)-6</b>	$\text{CH}_2\text{Cl}_2$	1000/1	r.t.	70	>99	98 (R)
9	<b>(R,R)-6</b>	$\text{CH}_2\text{Cl}_2$	1000/1	40	17	100	98 (R)
10	<b>(R,R)-6</b>	$\text{CH}_2\text{Cl}_2$	1000/1	50	10	100	98 (R)

<sup>a</sup>. Substrate concentration is 0.15 M. <sup>b</sup>. 5 equivalents of formic acid and 2 equivalents of  $\text{Et}_3\text{N}$ . <sup>c</sup>. S/C=100/1 reactions were carried out at rt, S/C=500/1-5000/1 reactions were carried out at 50 °C. <sup>d</sup>. Isolated yields. <sup>e</sup>. Ee values were determined by chiral HPLC, CHIRALPAK IB or IC column. <sup>f</sup>. Baseline separation not achieved by chiral HPLC.

solvents. <sup>c</sup>. Conversions were determined by  $^1\text{H}$  NMR. <sup>d</sup>. Ee values were determined by chiral HPLC, CHIRALPAK IB column.

Using the optimised conditions established above, the reductions of the derivatives of **4** were tested using catalyst **(R,R)-6** (Table 2). In several cases the S/C ratio could be increased to 1000/1 with no loss of ee compared to the S/C=100 reaction. The sense of reduction was assigned by comparison with known products where applicable (Ph, 4-nitrophenyl, 4-methoxyphenyl, thiienyl, furyl), and in all cases (including for R-Ph) the *R*-configuration product was formed from the **(R,R)**-catalyst, as illustrated. Other products were assigned by analogy. The selectivity matches that which would be predicted from the established  $\pi/\text{CH}$  edge/face directing effect of aryl-substituted substrates (Figure 1).<sup>9,10</sup>

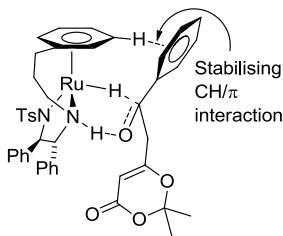
**Table 2.** Reduction of keto-dioxinones **4** using catalyst **(R,R)-6**.<sup>a,b,c</sup>



Entry	R	S/C	Yield (%) <sup>d</sup>	ee (%) <sup>e</sup>
1	Phenyl	1000/1	98	98 (R)
2	Phenyl	5000/1	93	98 (R)
3	4-Nitrophenyl	1000/1	82	95 (R)
4	4-Nitrophenyl	100/1	94	96 (R)
5	4-Methylphenyl	1000/1	92	98 (R)
6	4-Methylphenyl	100/1	96	97 (R)
7	3-Methylphenyl	1000/1	91	98 (R)
8	3-Methylphenyl	100/1	98	98 (R)
9	2-Methylphenyl	1000/1	94	>95 (R) <sup>f</sup>
10	2-Methylphenyl	100/1	90	>95 (R) <sup>f</sup>
11	4-Bromophenyl	1000/1	95	97 (R)
12	4-Bromophenyl	100/1	87	98 (R)
13	4-Methoxyphenyl	500/1	76	98 (R)
14	4-Methoxyphenyl	100/1	92	98 (R)
15	2-Thienyl	500/1	98	99 (R)
16	2-Thienyl	100/1	95	98 (R)
17	4-Fluorophenyl	1000/1	85	98 (R)
18	4-Fluorophenyl	100/1	98	99 (R)
19	2-Bromophenyl	100/1	88	82 (R)
20	2-Furyl	100/1	91	99 (R)

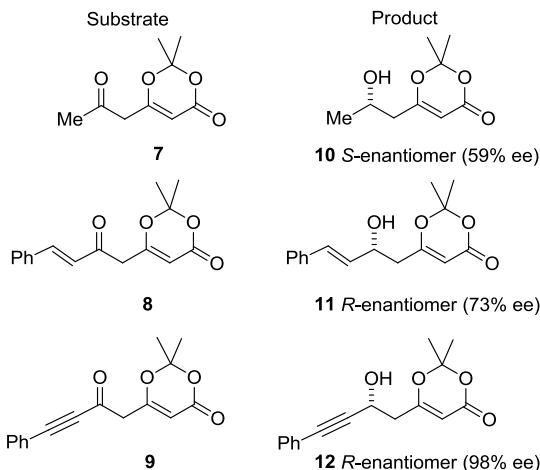
<sup>a</sup>. Substrate concentration is 0.15 M. <sup>b</sup>. 5 equivalents of formic acid and 2 equivalents of  $\text{Et}_3\text{N}$ . <sup>c</sup>. S/C=100/1 reactions were carried out at rt, S/C=500/1-5000/1 reactions were carried out at 50 °C. <sup>d</sup>. Isolated yields. <sup>e</sup>. Ee values were determined by chiral HPLC, CHIRALPAK IB or IC column. <sup>f</sup>. Baseline separation not achieved by chiral HPLC.

In order to investigate the directing group further, the reductions of derivatives of **4** with non-aromatic structures, i.e. **7-9**, were examined (Figure 2). High enantioselectivity was achieved using substrate **9**, containing a triple bond adjacent to the ketone, as would be expected given the known precedent for this group to act in the place of the aryl group, and the absolute configuration was assigned on this basis.<sup>11</sup>



**Figure 1.** Proposed orientation of substrate **4** ( $R = \text{Ph}$ ) during reduction by  $(R,R)$ -**6**.

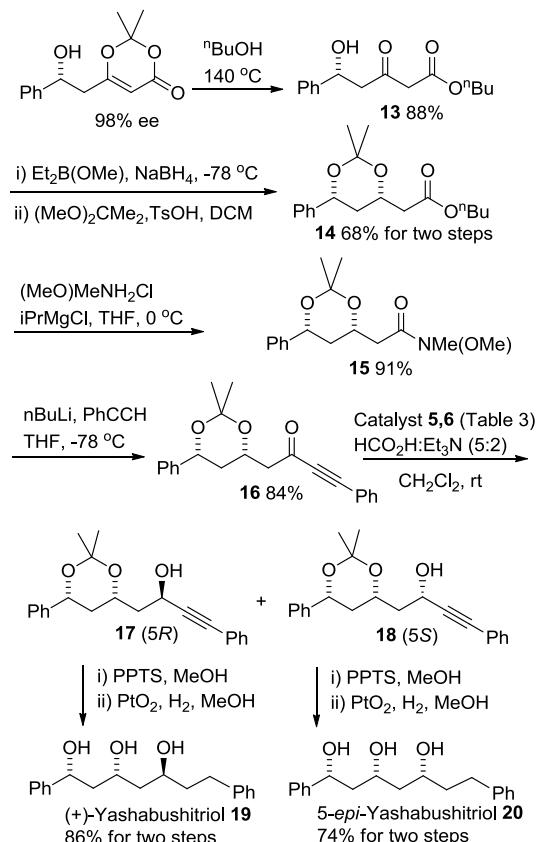
Alkene-containing substrate **8** gave a product **11** of lower ee but the same configuration. Methyl-substituted substrate **7** was reduced to **S-10** in 59% ee, though the hydride is delivered to the same ketone face compared to the other substrates, which indicates that this reduction was primarily controlled by steric factors.<sup>10i</sup> The absolute configurations of both **10** and **11** were assigned by comparison of their optical rotations to those previously reported (see Supporting Information).



**Figure 2.** Non-aromatic derivatives of **4** and their reduction products using  $(R,R)$ -**6** (conditions as for Table 2).

(+)-Yashabushitriol, a natural product first isolated in 1986, was identified as a suitable target for synthesis using the methodology reported above (Scheme 2).<sup>6</sup> Following ring opening<sup>2e</sup> to **13**, stereoselective reduction to the *syn* diol was required. This has been achieved by a number of methods<sup>4d</sup> including asymmetric transfer hydrogenation,<sup>4c</sup> however in our case the reduction using  $\text{Et}_2\text{B}(\text{OMe})$  and sodium borohydride<sup>2</sup> proved to be ideal and gave product **14** after diol protection in 5:1 distereoselectivity from which the major isomer could be purified by column chromatography (68% yield over two steps). The acetylenic ketone **16** was formed via **15**, and the opportunity was taken to study its reduction by ATH using catalysts **5** and **6**.<sup>11</sup> In the event, both catalysts gave excellent results with almost complete control of selectivity (Table 3). The extent of substrate selectivity could be gauged using a non-chiral

catalyst (Table 3, entry 6) and was found to be just 1:1.6 (**17:18**). Through this sequence, it was possible to prepare both (+)-yashabushitriol **19** and its 5-epimer **20** in enantiomerically pure form. The use of a second enantioselective reduction will ensure that the ee of the pure diastereoisomer in each case is high and greater than that of the substrate **16**.<sup>12</sup> The spectroscopic data of the (+)-yashabushitriol prepared by our route matched that of the reported material,<sup>6</sup> and the structure was additionally confirmed through an X-ray crystallographic study of our sample of **19** (Figure 3).<sup>13</sup>

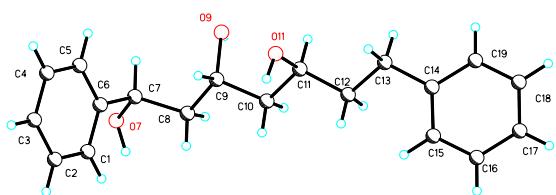


**Scheme 2.** Synthesis of (+)-yashabushitriol and its 5-epimer.

**Table 3.** Reductions of **16** using catalysts **5** and **6**.<sup>a</sup>

Entry	Catalyst	Catalyst loading (mol%)	dr ( <b>17:18</b> ) <sup>b</sup>	Isolated yield (%)
1	$(R,R)$ - <b>5</b>	5	10:1	99
2	$(S,S)$ - <b>5</b>	5	1:29	99
3	$(R,R)$ - <b>6</b>	1	37:1	94
4	$(R,R)$ - <b>6</b>	5	37:1	93
5	$(S,S)$ - <b>6</b>	5	1:30	99
6	$(\pm)$ -TsEN-Ru <sup>c</sup>	5	1:1.6	73

<sup>a</sup> 5 mol% catalyst, Substrate concentration is 0.12 M, r.t. <sup>b</sup> Dr values were determined by <sup>1</sup>H NMR. <sup>c</sup> Formed by combining  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]$  and  $\text{TsNHCH}_2\text{CH}_2\text{NH}_2$  in situ.



**Figure 3.** X-ray crystallographic structure of (+)-yashabushitriol **19** (CCDC 933463).<sup>13</sup>

There is relatively little precedent for the use of asymmetric reductions of 2,2-dimethyl-6-(2-oxoalkyl/oxoaryl)-1,3-dioxin-4-ones in synthetic applications. In related studies of asymmetric reductions of similar systems, compound **10** was formed in up to 90% ee using bakers' yeast,<sup>5a</sup> and a similar substrate similar to **7** containing an ester on the methyl group was reduced by a Ru/BINAP complex in up to 87% ee.<sup>5d</sup> As a component of a natural product synthesis, a diastereoselective reduction served to introduce a new chiral centre in high d.r.<sup>5e,f</sup> In this context we believe that this approach has potential for further synthetic applications.

In conclusion, we have found that the reduction of 2,2-dimethyl-6-(2-oxoaryl)-1,3-dioxin-4-ones can be achieved in high enantiomeric excess through ATH using Ru(II)/TsDPEN catalysts. An aromatic ring or triple bond adjacent to the ketone is required in order for products to be formed in high enantiomeric excess. The total synthesis of enantiomerically pure (+)-yashabushitriol was selected to highlight the synthetic value of the new methodology.

### Acknowledgments

We thank Warwick University for partial support of Y.F. and Johnson Matthey (Cambridge) for a generous gift of catalyst **6**. The X-ray diffraction instrument was obtained through the Science City Project with support from the AWM and part funded by the ERDF.

### Supplementary data

Experimental details, and characterisation data, <sup>1</sup>H and <sup>13</sup>C-NMR of all new compounds and chiral HPLC spectra.

### References

- (a) Scetti, A.; De Sio, V.; Villano, R.; Manzo, P.; Accocella, M. R. *Tetrahedron Lett.* **2010**, *51*, 3658-3661. (b) De Rosa, M.; Accocella, M. R.; Villano, R.; Soriente, A.; Scetti, A. *Tetrahedron: Asymmetry* **2003**, *14*, 2499-2500. (c) Accocella, M. R.; De Rosa, M.; Massa, A.; Polombi, L.; Villano, R.; Scetti, A. *Tetrahedron* **2005**, *61*, 4091-4097. (d) De Rosa, M.; Soriente, A.; Scetti, A. *Tetrahedron: Asymmetry* **2000**, *11*, 3187-3195. (e) Accocella, M. R.; Massa, A.; Polombi, L.; Villano, R.; Scetti, A. *Tetrahedron Lett.* **2005**, *46*, 6141-6144. (f) Ollevier, T.; Desyroy, V.; Catrinescu, C.; Wischert, R. *Tetrahedron Lett.* **2006**, *47*, 9089-9092. (g) Boulard, L.; BouzBouz, S.; Paris, J. M.; Cossy, J. *Synlett* **2007**, 1461-1463. (h) Jahn, U.; Hartmann, P.; Dix, I.; Jones, P. J. *Eur. J. Org. Chem.* **2002**, 718-735. (i) Sato, M.; Sugita, Y.; Abiko, Y.; Kaneko, C. *Tetrahedron: Asymmetry* **1992**, *3*, 1157-1160.
- (a) Krüger, J.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 7013-7016. (b) Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360-12361. (c) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837-838. (d) Zacharia, J. T.; Tanaka, T.; Hayashi, M. *J. Org. Chem.* **2010**, *75*, 7514-7518. (e) Szpilman, A. M.; Careghetti, D. M.; Manthorpe, J. M.; Wurtz, N. R.; Carreira, E. M. *Chem. Eur. J.* **2009**, *15*, 7117-7128. (f) Gademann, K.; Bethuel, Y.; Locher, H. H.; Hubschwerlen, C. *J. Org. Chem.* **2007**, *72*, 8361-8370. (g) Moreau, X.; Campagne, J.-M. *Tetrahedron Lett.* **2001**, *42*, 4467-4469. (h) Gademann, K.; Bethuel, Y. *Org. Lett.* **2004**, *6*, 4707-4710. (i) Aubele, D. L.; Wan, S.; Floreancig, P. E. **2005**, *44*, 3485-3488. (j) Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 7800-7801. (k) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774-3789. (l) Custar, D. W.; Zabawa, T. P.; Hines, J.; Crews, C. M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 12406-12414. (m) Custar, D. W.; Zabawa, T. P.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 804-805. (n) Gondi, V. B.; Gravel, M.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 5657-5660. (o) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Chem. Pharm. Bull.* **1994**, *42*, 839-845. (p) Sato, M.; Sakaki, J.-I.; Sugita, Y.; Yasuda, S.; Sakoda, H.; Kaneko, C. *Tetrahedron* **1991**, *47*, 5689-5708. (q) Yuan, Y.; Li, X.; Sun, J.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 14866-14867.
- (a) Hoye, T. R.; Danielson, M. E.; May, E.; Zhao, H. *J. Org. Chem.* **2010**, *75*, 7052-7060. (b) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396-10415. (c) Trost, B. M.; Gunzner, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 9449-9450.
- (a) Ngai, M. H.; Yang, P.-Y.; Liu, K.; Shen, Y.; Wenk, M. R.; Yao, A. Q.; Lear, M. J. *Chem. Commun.* **2010**, *46*, 8335-8337. (b) West, N. P.; Cergol, K. M.; Xue, M.; Randall, E. J.; Britton, W. J.; Payne, R. J. *Chem. Commun.* **2011**, *47*, 5166-5168. (c) Everaere, K.; Franceschini, N.; Mortreux, A.; Carpentier, J.-F. *Tetrahedron Lett.* **2002**, *43*, 2569-2571. (d) Wolberg, M.; Hummell, W.; Muller, M. *Chem. Eur. J.* **2001**, *7*, 4562-4571.
- (a) Sakaki, S.; Suzuki, M.; Kobayashi, S.; Sato, M.; Kaneko, C. *Chem. Lett.* **1990**, 901-904. (b) Sakaki, J.; Sugita, Y.; Sugita, Y.; Sato, M.; Kaneko, C. *Chem. Commun.* **1991**, 434-435. (c) Sugita, Y.; Sakaki, J.; Sato, M.; Kaneko, C. *Org. Biomol. Chem.* **1992**, 2855-2861. (d) Kiegiel, J.; Józwik, J.; Woźniak, K.; Jurczak, J. *Tetrahedron Lett.* **2000**, *41*, 4959-4963. (e) Munakata, R.; Katakai, H.; Ueki, T.; Kurosaka, J.; Takao, K.; Tadano, K. *J. Am. Chem. Soc.* **2003**, *125*, 14722-14722. (f) Munakata, R.; Katakai, H.; Ueki, T.; Kurosaka, J.; Takao, K.; Tadano, K. *J. Am. Chem. Soc.* **2004**, *126*, 11254-11267.
- (a) Hashimoto, T.; Tori, M.; Asakawa, Y. *Chem. Pharm. Bull.* **1986**, *34*, 1846-1849. (b) Feldman, K. S.; Simpson, R. E. *Tetrahedron Lett.* **1989**, *30*, 6985-6988. (c) Miyashita, M.; Hoshino, M.; Yoshikoshi, A. *Chem. Lett.* **1990**, 791-794.
- (a) Jacques, A. A.; Patel, B. H.; Barrett, A. G. M. *Tetrahedron Lett.* **2011**, *52*, 6072-6075. (b) Anderson, K.;

- Calo, F.; Pfaffeneder, T.; White, A. J. P.; Barrett, A. G. M. *Org. Lett.* **2011**, *13*, 5748-4750. (c) Patel, B. H.; Mason, A. M.; Barrett, A. G. M. *Org. Lett.* **2011**, *13*, 5156-5159. (d) Patel, B. H.; Mason, A. M.; Patel, H.; Coombes, R. C.; Simak, A.; Barrett A. G. M. *J. Org. Chem.* **2011**, *76*, 6209-6217. (e) Cordes, J.; Calo, F.; Anderson, K.; Pfaffeneder, T.; Laclef, S.; White, A. J. P.; Barrett, A. G. M. *J. Org. Chem.* **2012**, *77*, 652-657. (f) Calo, F.; Richardson, J.; Barrett, A. G. M. *Org. Lett.* **2009**, *11*, 4910-4913. (g) Nacarro, I.; Bassett, J.-F.; Hebbe, S.; Major, S. M.; Werner, T.; Howsham, C.; Bräklow, J.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2008**, *130*, 10293-10298. (h) Katritzky, A. R.; Wang, Z.; Wang, M.; Hall, C. D.; Suzuki, K. *J. Org. Chem.* **2005**, *70*, 4854-4856.
8. (a) Munakata, R.; Katakai, H.; Ueki, T.; Kurosaka, J.; Takao, K.; Tadano, K.; *J. Am. Chem. Soc.* **2004**, *126*, 11254-11267. (b) Munakata, R.; Katakai, H.; Ueki, T.; Kurosaka, J.; Takao, K.; Tadano, K. *J. Am. Chem. Soc.* **2003**, *125*, 14722-14723. (c) Bach, T.; Krsch, S. *Synlett* **2001**, 1974-1976.
9. (a) Hashiguchi, S.; Noyori, R. *Acc. Chem. Res.* **1997**, *30*, 97-102. (b) Clapham, S. E.; Hadzovic, A.; Morris, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2201-2237. (c) Gladiali, S.; Alberrico, E. *Chem. Soc. Rev.* **2006**, *35*, 226-236. (d) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393-406. (e) Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300-1308. (f) Wang, C.; Wu, X.; Xiao, J. *Chem. Asian J.* **2008**, *3*, 1750-1770.
10. (a) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562-7563. (b) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521-2522. (c) Haack, K. J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed.* **1997**, *36*, 285-288. (d) Murata, K.; Okano, K.; Miyagi, M.; Iwane, H.; Noyori, R.; Ikariya, T. *Org. Lett.* **1999**, *1*, 1119-1121. (e) Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G. *J. Am. Chem. Soc.* **1999**, *121*, 9580-9588. (f) Handgraaf, J.-W.; Meijer, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 3099-3103. (g) Soni, R.; Cheung, F. K.; Clarkson, G. C.; Martins, J. E. D.; Graham, M. A.; Wills, M. *Org. Biomol. Chem.* **2011**, *9*, 3290-3294. (h) Steward, K. M.; Gentry, E. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2012**, *134*, 7329-7332. (i) Cheung, F. K.; Lin, C.; Minissi, F.; Lorente Crivillé, A.; Graham, M. A.; Fox, D. J.; Wills, M. *Org. Lett.* **2007**, *9*, 4659-4662. (j) Soni, R.; Collinson, J.-M.; Clarkson, G. J.; Wills, M. *Org. Lett.* **2011**, *13*, 4304-4307. (k) Hems, W. P.; Jackson, W. P.; Nightingale, P.; Bryant, R. *Org. Process Res. Dev.* **2012**, *16*, 461-463. (l) Kumaraswamy, G.; Ramakrishna, G.; Sridhar, B. *Tetrahedron Lett.* **2011**, *52*, 1778-1782. (m) Liu, Z.; Schultz, C. S.; Sherwood, C. A.; Krska, S.; Dormer, P. G.; Desmond, R.; Lee, C.; Sherer, E. C.; Shpungin, J.; Cuff, J.; Xu, F. *Tetrahedron Lett.* **2011**, *52*, 1685-1688. (n) Seashore-Ludlow, B.; Villo, P. Somfai, *Chem. Eur. J.* **2012**, *18*, 7219-7223. (o) Limanto, J.; Krska, S. W.; Dorner, B. T.; Vazquez, E.; Yoshikawa, N.; Tan, L. *Org. Lett.* **2010**, *12*, 512-515.
11. (a) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738-8739. (b) Chavez, D. E.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2001**, *40*, 3667-3670. (c) Bogliotti, N.; Dalko, P. I.; Cossy, J. *Tetrahedron Lett.* **2005**, *46*, 6915-6918. (d) Marshall, J. A.; Eidam, P.; Eidam, H. S. *J. Org. Chem.* **2006**, *71*, 4840-4844. (e) Xing, Y.; O'Doherty, G. A. *Org. Lett.* **2009**, *11*, 1107-1110. (f) Daniels, D. S. B.; Thompson, A. L.; Anderson, E. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 11506-11510. (g) Gagnepain, J.; Moulin, E.; A. Fürstner, A. *Chem. Eur. J.* **2011**, *17*, 6964-6972. (h) Nakayama, A.; Kogure, N.; Kitayama, M.; Takayama, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 8025-8028. (i) Druais, V.; Meyer, C.; Cossy, J. *Org. Lett.* **2012**, *14*, 516-519 (j) Dias, L. C.; Ferreira, M. A. B. *J. Org. Chem.* **2012**, *77*, 4046-4062. (k) Gallon, J.; Esteban, J.; Bouzbouz, S.; Campbell, M.; Reymond, S.; Cossy, J. *Chem. Eur. J.* **2012**, *18*, 11788-11797. (l) Mi, X.; Wang, Y.; Zhu, L.; Wang, R.; Hong, R. *Synthesis* **2012**, *44*, 3432-3440. (m) Arai, N.; Satoh, H.; Utsumi, N.; Murata, K.; Tsutsumi, K.; Ohkuma, T. *Org. Lett.* **2013**, *15*, 3030-3033. (n) Raghavan, S.; Vinoth Kumar, V. *Org. Biomol. Chem.* **2013**, *11*, 2847-2858. (o) Kesava Reddy, N.; Chandrasekhar, S. *J. Org. Chem.* **2013**, *78*, 3355-3360
12. Vigneron J. P.; Dhaenens M.; Horeau A. *Tetrahedron* **1973**, *29*, 1055-1059.
13. X-ray data for (+)-yashabushitriol (CCDC 933463);  $C_{19}H_{24}O_3$ ,  $M = 300.38$ , Monoclinic, space group  $P2(1)$ ,  $a = 9.32711(10)$ ,  $b = 5.70755(6)$ ,  $c = 15.13134(16)$  Å,  $\alpha = 90^\circ$ ,  $\beta = 91.5550(10)^\circ$ ,  $\gamma = 90^\circ$ ,  $U = 805.220(15)$  Å $^3$  (by least squares refinement on 5461 reflection positions),  $T = 150(2)$  K,  $\lambda = 1.54184$  Å,  $Z = 2$ ,  $D(\text{cal}) = 1.239$  Mg/m $^3$ ,  $F(000) = 324$ .  $\mu(\text{MoK}-\alpha) = 0.655$  mm $^{-1}$ . Crystal character: colourless block. Crystal dimensions 0.45 x 0.20 x 0.12 mm. Full details are given in the supporting information.