Highly enantioselective synthesis of angelmarin†

Hang Jiang and Yasumasa Hamada*

Received 6th July 2009, Accepted 23rd July 2009
First published as an Advance Article on the web 4th August 2009
DOI: 10.1039/b913400j

Angelmarin (1), a novel anti-cancer agent, was efficiently synthesized through a highly enantioselective epoxidation and a copper cyanide-mediated esterification of the hindered alcohol as the key steps in 53% overall yield.

During the course of a unique screening program using the anti-austerity strategy,[1-3] Kadota, Esumi, and co-workers identified a new coumarin natural product, angelmarin (**1**),[4] from an extract of *Angelica pubescens*, which preferentially displays strong activity against PANC-1 cancer cells under a nutrient starvation environment (Fig. 1). Its core structure is columbianetin (**2**) with a 2-substituted benzofuran moiety, which occurs widely in many natural products of plant origin.[5] Based on its interesting anti-tumor activity as well as the scarcity of an efficient method for the construction of optically active 2-substituted benzofurans,[6] we decided to attempt the synthesis of this natural product. A recent publication of the synthesis of (+)-**1** by Coster and Magolan[7] prompted us to disclose our efforts on the synthesis of **1**. Our synthesis of angelmarin contains a highly enantioselective epoxidation and an efficient copper-mediated esterification as the key steps. Our method is superior to the reported one with regard to its efficiency and enantioselectivity.

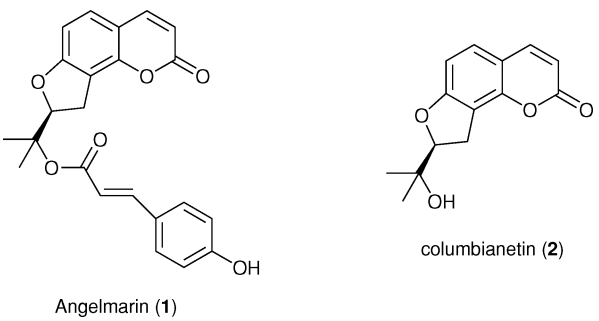
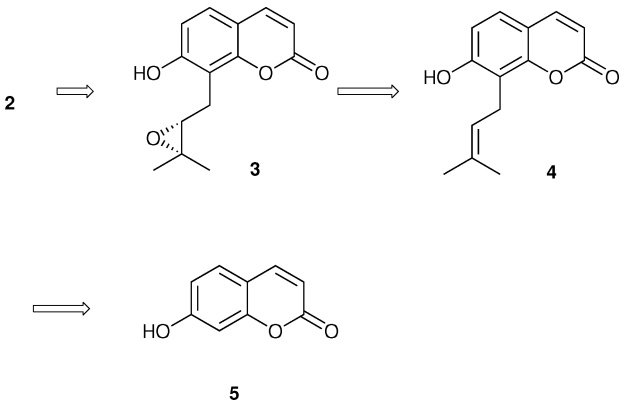
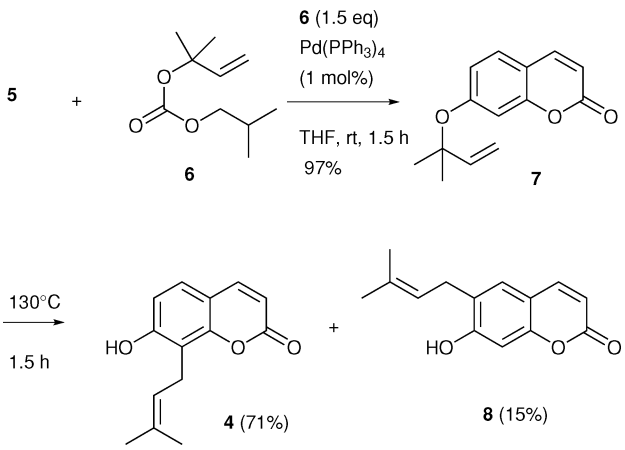


Fig. 1 Angelmarin and columbianetin.

The obvious route to **2** is the enantioselective epoxidation of 7-hydroxy-8-prenylcoumarin (osthenol, **4**), which is derived from the commercially available 7-hydroxycoumarin (**5**) through the Claisen rearrangement (Scheme 1). The precursor **7** for the Claisen rearrangement is conventionally derived from the 2-(2-methyl)-but-3-ynylation of **5** and subsequent hydrogenation using the Lindlar catalyst.[8] However, **7** could be conveniently prepared from **5** by the palladium-catalyzed direct allylation using the mixed carbonate **6** in high yield (Scheme 2).[9]



Scheme 1



Scheme 2

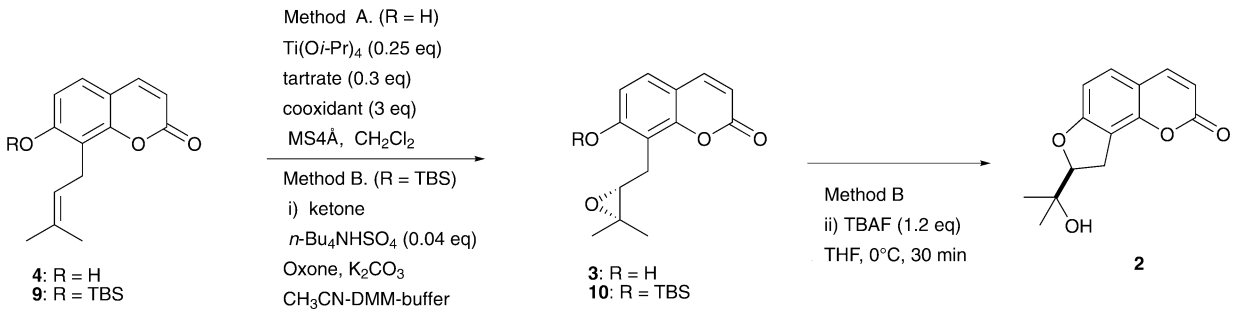
According to the precedent,[8] **7** was heated at 130 °C for 1.5 h to give a separable mixture of the desired **4** and its isomer **8** in an 86/14 ratio. After the chromatographic separation of the mixture, we examined the enantioselective construction of the benzofuran moiety using pure **4**. The authentic racemic columbianetin was obtained according to Franke's method.[10] The enantioselective epoxidation of **4** and its derivative is shown in Table 1.

First, we investigated the Sharpless asymmetric epoxidation using titanium tetraisopropoxide and tartrates (entries 1–3). Although we extensively surveyed the reaction conditions, we were unable to obtain a satisfactory result. The enantioselectivity was moderate (~69% ee) and the yield was low due to the production of the side product **11**, which was formed by the titanium tetraisopropoxide-induced ring opening reaction of the product epoxide. After some experiments, we succeeded in the suppression of this side reaction by changing the oxidant from TBHP to tritylhydroperoxide (TPHP), a bulkyl peroxide, but the reactivity was slower than that of TBHP and the chemical yield

Yayoi-cho, Inage-ku, Chiba 263-8522, Japan. E-mail: hamada@p.chiba-u.ac.jp; Fax: +81-43-290-2987; Tel: +81-43-290-2987

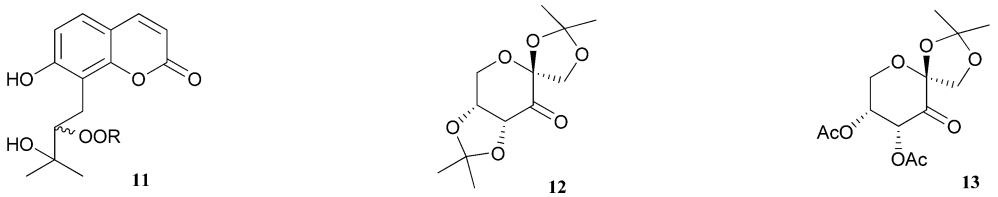
† Electronic supplementary information (ESI) available: Experimental and NMR data of compounds; copies of ^{1}H NMR and ^{13}C NMR spectra of compounds. See DOI: 10.1039/b913400j

Table 1 Enantioselective epoxidation



Entry	Substrate	Reagents (eq.)	Conditions	Yield[a]	% ee[b]
1	**4**	method A, DMT-TBHP	−20 °C, 87 h	31[c]	68
2	**4**	method A, DET-CHP	0 °C, 17.5 h	27[d]	61
3	**4**	method A, DET-TPHP	−20 °C, 89 h	38[e]	69
4	**4**	method B[f], ketone **12** (0.3)	−10 °C, 4 h	28[g]	21
5	**9**	method B[f], ketone **12** (0.3)	0 °C, 3 h	25[g]	77
6	**9**	method B[h], ketone **13** (0.15)	0 °C, 23 h	88[g]	97

[a] Isolated yield. [b] Enantiomeric excess of **2**. [c] Yield of **11** (R = *t*-Bu): 56%. [d] Yield of **11** (R = Cumenyl): 67%. [e] Yield of **11** (R = trityl): trace. [f] Oxone (1.38 eq.), K_2CO_3 (5.8 eq.), CH_3CN–DMM–buffer (1/2/2). Buffer: 0.05 M solution of $Na_2B_4O_7$ $10H_2O$ in 4×10^{-4} M aqueous Na_2(EDTA). [g] Yield of two steps. [h] Oxone (1.63 eq.), K_2CO_3 (2.4 eq.), CH_3CN–DMM–buffer (1.8/3.6/1). Buffer: 0.1 M aqueous KOH/0.1 M aqueous KH_2PO_4/H_2O = 5.6/50/44.4, pH 6.

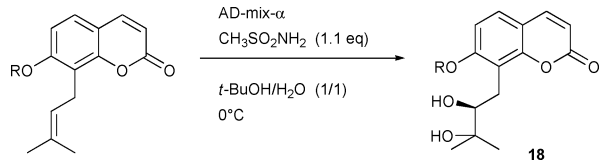


was still unsatisfactory. Next, we turned our attention to the Shi epoxidation[11] using the chiral dioxirane generated from a ketone and Oxone. The epoxidation of **4** using the ketone **12** under the standard Shi conditions at −10 °C for 4 h directly afforded the cyclized **2** in 28% yield (entry 4). The enantioselectivity was disappointedly low (21% ee). After some preliminary experiments, we found that the protection of the phenolic function with a silyl group significantly enhanced the enantioselectivity (entry 5). The protection of **4** with *tert*-butylchlorodimethylsilane and imidazole in dimethylformamide at rt for 1.5 h gave the silylated **9** in a quantitative yield. The thus-obtained **9** was subjected to the Shi epoxidation using a catalytic amount of tetra-*n*-butylammonium hydrogen sulfate and the chiral ketone **12** (0.3 equiv.) in the presence of an excess amount of Oxone (1.38 equiv.) and potassium carbonate (5.8 equiv.) in a mixed solvent of acetonitrile, dimethoxymethane (DMM), and buffer[12] at 0 °C for 3 h, yielding a mixture of the target epoxide **10** and the starting material with a 25/75 ratio. Treatment of the crude epoxidized product with tetra-*n*-butylammonium fluoride (TBAF) in tetrahydrofuran (THF) at 0 °C for 30 min afforded **2** with a 77% ee in 25% yield. Since the enantioselectivity and chemical yield by the Shi epoxidation method were still unsatisfactory, we surveyed other ketones for this transformation. In 2005, Vidal-Ferran and co-workers reported a Shi-type ketone **13** for epoxidations, which is robust and equally effective when compared to the ketone **12**.[13] Surprisingly, for the epoxidation of **9** the Vidal-Ferran's ketone **13** was superior to **12** and afforded, after treatment of the epoxide with TBAF, columbianetin **2** with a 97% ee in 88% yield (two steps). In contrast to the original Shi procedure, lower catalyst loadings (15 mol%) and a smooth reaction were possible without any loss of reaction efficiency. The optically pure **2** could be obtained by one recrystallization from ethyl acetate. To demonstrate the preparative utility of this new asymmetric synthesis, the epoxidation–fluoride anion-induced cyclization process was performed on a 10 gram-scale to afford columbianetin (+)-**2** with almost the same efficiency of 97% ee in 85% yield.‡

As an alternative route for the preparation of the optically active **2**, we briefly investigated the Sharpless enantioselective dihydroxylation of **4** and its derivatives as shown in Table 2. Interestingly, the enantioselectivity was strongly dependent on the phenolic protecting group employed. Sulfonyl groups caused negative effects concerning the enantioselectivity (entries 2 and 5). In the case of the triflate **14**, the reaction directly produced the cyclized **2** in 16.4% yield, which apparently arose from the intramolecular aromatic nucleophilic substitution of the diol **18** (R = Tf). The benzyl and acetyl groups largely enhanced the enantioselectivity (entries 3 and 4). Although the route using the asymmetric dihydroxylation was attractive, we selected the more efficient pathway above using the asymmetric epoxidation.

The final task remaining in the synthesis of angelmarin (**1**) was the esterification of the tertiary alcohol of **2** with *p*-hydroxycinnamic acid. We carried out model experiments using (*rac*)-**2** and tiglic acid as shown in Table 3. The reaction using either the usual condensing agents or the Mitsunobu procedure did

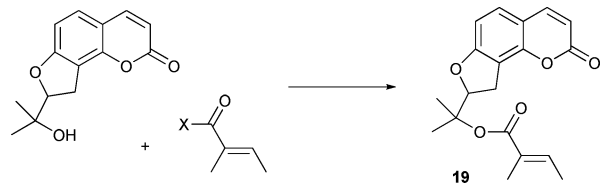
Table 2 Enantioselective dihydroxylation[a]



Entry	Substrate	Time (h)	Yield (%)[b]	% ee
1	**4** (R = H)	4	19	50
2	**14** (R = Tf)	10	19[c]	0
3	**15** (R = Bn)	24	69	80
4	**16** (R = Ac)	42	20	88
5[d]	**17** (R = Ns)	8	68	6

[a] AD-mix-α (140 mg/0.1 mmol). [b] Isolated yield. [c] The cyclized product **2** was obtained in 16.4%. [d] The reaction was carried out in 50% aqueous *t*-BuOH/CH_2Cl_2 (1/1).

Table 3 Reaction conditions for esterification

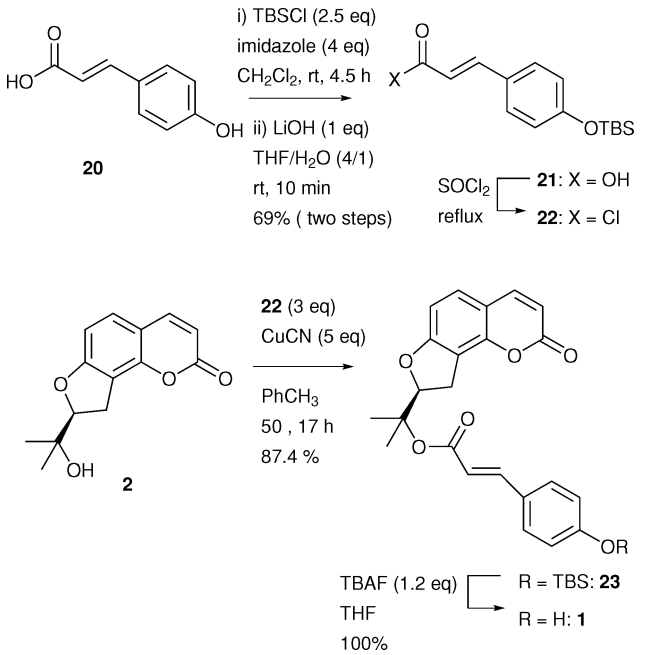


Entry	X (eq.)	Conditions	Yield (%)[a]
1	OH (2)	DCC–DMAP, CH_2Cl_2, rt, 24 h	nr
2	OH (1)	DEAD–PPh_3, THF, rt, 24 h	nr
3	Cl (1)	pyridine, rt, 10 h	nr
4	Cl (2)	*n*-BuLi, THF, −78 °C to rt, 24 h	nr
5	Cl (1.5)	NaH, THF, 0 °C to rt, 24 h	nr
6	Cl (10)	AgCN (15 eq.), $PhCH_3$, 50 °C, 72 h	100
7	Cl (2)	AgCN (3 eq.), $PhCH_3$, 50 °C, 26 h	91[b]
8	Cl (2)	CuCN (3 eq.), $PhCH_3$, 50 °C, 26 h	91[b]

[a] Isolated yield. [b] A small amount of **2** was recovered.

not take place and the starting material was completely recovered (entries 1 and 2). The acid chloride in combination with bases resulted in no reaction (entries 3–5). Finally, we found that the addition of silver cyanide or cuprous cyanide as a base to the solution of the acid chloride effectively provided the corresponding ester **19** in high yield (entries 6–8).[14] The cheap cuprous cyanide method is preferable based on the cost.§

As illustrated in Scheme 3, the required acid chloride **22** for the final construction of **1** was obtained from **20** by (1) the protection of the phenolic hydroxyl group and carboxylic function with *tert*-butylchlorodimethylsilane and imidazole, (2) the selective removal of the silyl ester with lithium hydroxide in aqueous THF, and (3) the treatment of the carboxylic acid **21** with refluxing thionyl chloride. The esterification of **2** with the acid chloride **22** proceeded smoothly in the presence of an excess amount of cuprous cyanide (5 equiv.) in toluene at 50 °C for 17 h to afford the ester **23** in 87.4% yield. Final deprotection of **23** with TBAF (1.2 equiv.) in THF furnished angelmarin (**1**) in a quantitative yield.[15] This asymmetric synthesis of **1** is the most efficient method so far and the overall yield is 53% in six steps from the commercially available **5**.



Scheme 3

In conclusion, we have established the efficient asymmetric synthesis of angelmarin (**1**), which ensures the supply of the optically pure **1**. Using this method, many analogs of **1** will be available for evaluation of their biological activities. Further investigations into the formation of 2-substituted benzofurans and the structure–activity relationship of angelmarin and its analogs are underway.

Acknowledgements

This work was financially supported in part by Special Funds for Education and Research (Development of SPECT Probes for Pharmaceutical Innovation) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Notes and references

‡ Typical procedure for the synthesis of (+)-**2** from **9**: Alkene **9** (10.0 g, 29.0 mmol) and ketone **13** (1.32 g, 4.35 mmol) were dissolved in acetonitrile (192 mL) and dimethoxymethane (384 mL). A buffer (pH 6, made from 0.1 M aqueous KOH/0.1 M aqueous KH_2PO_4/H_2O = 5.6/50/44.4) solution (105 mL) and tetra-*n*-butylammonium hydrogen sulfate (0.39 g, 1.16 mmol) were slowly added with stirring, and the mixture was cooled to 0 °C. The flask was equipped with two dropping funnels; one of them was filled with a solution of Oxone (29.1 g, 47.3 mmol) in the buffer solution (pH 6, 183 mL), and the other one with a solution of K_2CO_3 (9.63 g, 69.7 mmol) in water (183 mL). The two solutions were added dropwise over 4 h. The reaction mixture was stirred at 0 °C for another 43.5 h. The reaction mixture was then quenched by the addition of water (500 mL) and *n*-hexane (150 mL) and extracted with *n*-hexane (300 mL × 2). The combined organic extracts were washed with brine (300 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was used without purification. The above residue was dissolved in THF (100 mL), and TBAF (1 M in THF, 34.8 mL) was added at 0 °C with stirring. The reaction mixture was gradually warmed to room temperature. After being stirred for 4 h, the mixture was diluted with ethyl acetate, washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 1/1) to give columbianetin (**2**, 6.07 g, 84.9%) as a colorless solid. Recrystallization from ethyl acetate provided the optically

pure **2** (100% ee judged by HPLC): mp 161–162 °C; $[\alpha]_D^{25}$ +183.55 (*c* 1.0, $CHCl_3$) (lit.[4] $[\alpha]_D^{25}$ +198 (*c* 0.025, $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.37 (s, 3H) 3.32 (m, 2H), 4.80 (t, J = 8.8 Hz, 1H), 6.21 (d, J = 9.6 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 9.6 Hz, 1H): ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 26.0, 27.6, 71.8, 91.3, 106.7, 112.3, 113.1, 114.0, 128.7, 144.0, 151.3, 161.0, 163.7; IR (KBr, cm^{-1}) 3502, 2969, 1698, 1609, 1490, 1453, 1406, 1337, 1316, 1254, 1146, 1118, 1065, 1011, 946, 826, 779, 759; HRMS (FAB) calcd for $C_{14}H_{15}O_4$: 247.0970 $[M + H]^+$. Found: 247.0956. HPLC analysis using CHIRALPAC AD and *n*-hexane/*i*-PrOH (75:25, 0.5 mL min^{-1}), Retention time for major: 15.6 min; minor: 22.9 min. 97% ee.

§ Typical procedure for the copper cyanide-mediated esterification: To a stirred suspension of **2** (400 mg, 1.62 mmol, 100% ee) and CuCN (727 mg, 8.12 mmol) in toluene (5 mL) at room temperature was added a solution of the acid chloride **22** (4.87 mmol) in toluene (10 mL). After being stirred for 18.5 h at 50 °C, the mixture was filtered through a Celite pad and the insoluble material was washed with ethyl acetate. The combined filtrates were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 3/1) to give **23** (719.5 mg, 87.4%) as a brown oil.

1 K. Izuishi, K. Kato, T. Ogura, T. Kinoshita and H. Esumi, *Cancer Res.*, 2000, **60**, 6201.

2 J. Lu, S. Kunimoto, Y. Yamazaki, M. Kaminishi and H. Esumi, *Cancer Sci.*, 2004, **95**, 547.

3 S. Awale, J. Lu, S. K. Kalauni, Y. Kurashima, Y. Tezuka, S. Kadota and H. Esumi, *Cancer Res.*, 2006, **66**, 1751.

4 S. Awale, E. M. N. Nakashima, S. K. Kalauni, Y. Tezuka, Y. Kurashima, J. Lu, H. Esumi and S. Kadota, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 581.

5 For reviews of naturally occurring coumarins, see: (*a*) R. D. H. Murray, in *Progress in the Chemistry of Organic Natural Products*, eds. W. Herz, G. W. Kirby, W. Steglich, and Ch. Tamm, Springer-Verlag, Wien New York, 1991, **58**, 83–316; (*b*) R. D. H. Murray, in *Progress in the Chemistry of Organic Natural Products*, eds. W. Herz, G. W. Kirby, R. E. Moore, W. Steglich, and Ch. Tamm, Springer-Verlag, Wien New York, 1997, **72**, 2–119.

6 For the enantioselective synthesis of the optically active 2-substituted benzofurans, see: (*a*) T. Hosokawa, T. Uno, S. Inui and S. Murahashi, *J. Am. Chem. Soc.*, 1981, **103**, 2318; (*b*) T. Hosokawa, Y. Imada and S. Murahashi, *Bull. Chem. Soc. Jpn*, 1985, **58**, 3282; (*c*) T. Hosokawa, T. Kono, T. Shinohara and S. Murahashi, *J. Organomet. Chem.*, 1989, **370**, C13; (*d*) Y. Uozumi, K. Kato and T. Hayashi, *J. Am. Chem. Soc.*, 1997, **119**, 5063; (*e*) Y. Uozumi, H. Kyota, K. Kato, M. Ogasawara and T. Hayashi, *J. Org. Chem.*, 1999, **64**, 1620; (*f*) T. Nemoto, T. Ohshima and M. Shibasaki, *Tetrahedron Lett.*, 2000, **41**, 9569; (*g*) T. Nemoto, T. Ohshima and M. Shibasaki, *Tetrahedron*, 2003, **59**, 6889; (*h*) Y. Natori, H. Tsutsui, N. Sato, S. Nakamura, H. Nambu, M. Shiro and S. Hashimoto, *J. Org. Chem.*, 2009, **74**, 4418.

7 J. Magolan and M. J. Coster, *J. Org. Chem.*, 2009, **74**, 5083.

8 R. D. H. Murray, M. M. Ballantyne and K. P. Mathai, *Tetrahedron*, 1971, **27**, 1247.

9 For the 3-(3-methyl)-but-1-enylation of phenols, see: T. Kaiho, T. Yokoyama, H. Mori, J. Fujiwara, T. Nobori, H. Odaka, J. Kamiya, M. Maruyama, and T. Sugawara, JP 06128238, 1994; [*Chem. Abs.*, 1995, **123**, 55900].

10 F. Bohlmann and H. Franke, *Chem. Ber.*, 1971, **104**, 3229.

11 (*a*) Y. Tu, Z.-X. Wang and Y. Shi, *J. Am. Chem. Soc.*, 1996, **118**, 9806; (*b*) Z.-X. Wang, Y. Tu, M. Frohn, J.-R. Zhang and Y. Shi, *J. Am. Chem. Soc.*, 1997, **119**, 11224.

12 Buffer: 0.05 M solution of $Na_2B_4O_7$ 10 H_2O in 4×10^{-4} M aqueous Na_2(EDTA).

13 (*a*) N. Nieto, P. Molas, J. Benet-Buchholz and A. Vidal-Ferran, *J. Org. Chem.*, 2005, **70**, 10143; (*b*) B. Wang, X.-Y. Wu, O. A. Wong, B. Nettles, M.-X. Zhao, D. Chen and Y. Shi, *J. Org. Chem.*, 2009, **74**, 3986.

14 For silver cyanide-mediated esterification, see: (*a*) S. Takimoto, J. Inanaga, T. Katsuki and M. Yamaguchi, *Bull. Chem. Soc. Jpn*, 1976, **49**, 2335; (*b*) S. Hara, K. Makino and Y. Hamada, *Tetrahedron Lett*, 2006, **47**, 1081.

15 **1** as amorphous solids: $[\alpha]_D^{25}$ + 237.8 (*c* 1.025, $CHCl_3$), $[\alpha]_D^{25}$ + 217.5 (*c* 0.028, $CHCl_3$) (lit.[4] $[\alpha]_D^{25}$ + 218.7 (*c* 0.025, $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.65 (s, 3H), 3.39 (m, 2H), 5.20 (t, J = 9.6 Hz, 1H), 6.15 (d, J = 16.0 Hz, 1H), 6.24 (d, J = 9.2 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 7.30 (m, 3H), 7.35 (d, J = 15.6 Hz, 1H), 7.67 (d, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 22.1, 27.6, 82.2, 89.1, 106.9, 112.1, 113.0, 113.6, 115.9, 116.4, 126.9, 128.9, 129.9, 144.2, 144.4, 151.2, 158.0, 161.4, 164.1, 166.4; IR (KBr, cm^{-1}) 3303, 1696, 1602, 1513, 1489, 1455, 1406, 1387, 1369, 1328, 1260, 1200, 1167, 1118, 1065, 976, 871, 828, 753; HRMSFAB calcd for $C_{23}H_{21}O_6$ 393.1338 $[M + H]^+$, found 393.1321.

