Tetrahedron: *Asymmetry* 22 (2011) 4–7

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Efficient and practical asymmetric synthesis of isopropyl (*R*)-3-(3′,4′-dihydroxyphenyl)-2-hydroxypropanoate and its enantiomer

Ming Chen [a,†], Hui Chen [a,†], Yuzhen Wang [a], Haibo Wang [a], Yefei Nan [b], Xiaohui Zheng [b,*], Ru Jiang [a,*]

[a] *Department of Medicinal Chemistry and Pharmaceutical analysis, School of Pharmacy, Fourth Military Medical University, Xi'an 710032, China*
[b] *Key Laboratory of Resource Biology and Biotechnology in Western China and College of Life Sciences, Northwest University, Xi'an 710069, China*

ARTICLE INFO

Article history:
Received 19 October 2010
Accepted 24 November 2010
Available online 31 January 2011

ABSTRACT

The highly enantioselective synthesis of (*R*)-isopropyl 3-(3′,4′-dihydroxyphenyl)-2-hydroxypropanoate and its enantiomer has been achieved starting from 3,4-dihydroxybenzaldehyde. The stereogenic centers were established through asymmetric dihydroxylation of (*E*)-isopropyl 3,4-bis(benzyloxy) cinnamate. A convenient manipulation in selective catalytic hydrogenation and deprotection was also accomplished in HCl–^{i}PrOH employing 10% Pd/C catalyst.

1. Introduction

Danshen, the dried root of *Salvia miltiorrhiza*, is a traditional Chinese medicine widely used for the treatment of cardiovascular diseases in China and other countries.[1] The extract of danshen was approved by the Chinese State Food and Drug Administration as an activating blood circulation agent with the trade name of Danshen Tablet (state drug permit doc: Z20055235). More than 50 chemical constituents of danshen have been identified and shown to possess various biological and pharmacological effects, including improvement of microcirculation, anti-blood coagulation, anti-oxidation, anti-myocardial ischemia, anti-inflammation, and anti-neoplasticity.[2–8] In 2007, we found a new metabolite of danshen after oral administration of the compound Danshen Dripping pills (state drug permit doc: Z10950111), a novel compound, namely isopropyl 3-(3′,4′-dihydroxyphenyl)-2-hydroxypropanoate (IDHP, Fig. 1).[9] Further studies have proved that IDHP exerts a vasorelaxant effect by inhibiting both Ca^{2+} release from intracellular stores and Ca^{2+} influx through voltage-dependent calcium channels and receptor-operated calcium channels in vascular smooth muscle cells.[10] Moreover, it also exhibited a significant neuroprotective effect on MCAO-induced focal cerebral ischemia by inhibiting lipid peroxidation, increasing endogenous antioxidant defense enzymes, and improving brain mitochondrial energy metabolism.[11] These findings indicated that IDHP might be developed as a new medicine for the treatment of cardiovascular and cerebrovascular diseases. Therefore, it is necessary to assess the contributions of the different stereoisomers to the pharmacodynamics and pharmacokinetics, respectively, for IDHP. The aim of the present study was, therefore, to establish a concise and practical synthesis method of (*R*)/(*S*)-IDHP.

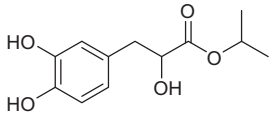


Figure 1. Structure of IDHP.

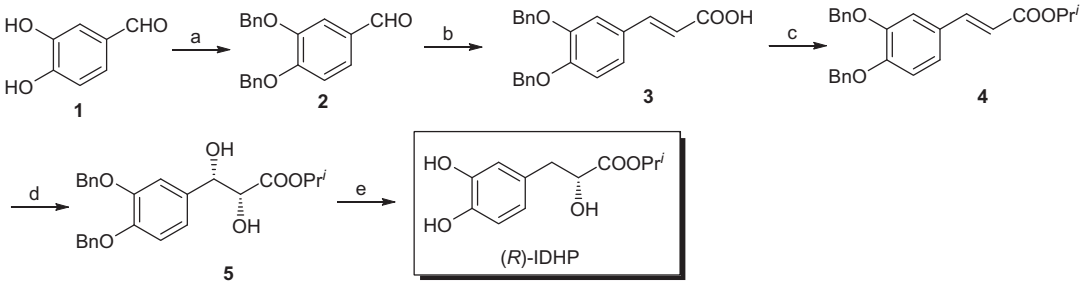
2. Results and discussion

The strategies for the preparation of chiral α-hydroxy esters involve the stereoselective oxidation of a pro-chiral ester by a camphoryl-sulfonyloxaziridine, alkylation of chiral glycolate enolates, and catalytic hydrogenation of enol esters, and α-keto acid derivatives.[12–15] The method we adopted is based on the Sharpless catalytic asymmetric dihydroxylation (AD) reaction of substituted (*E*)-cinnamates.[16–18] Cinnamates, which can be readily prepared from aldehyde, have proven to be exceptionally good substrates for the AD reaction. The resulting α,β-dihydroxy esters are obtained with high enantiomeric excesses and good yield. The subsequent selective deoxygenation of the β-hydroxyl group provides the desired product. Therefore, we designed the following synthetic route to (*R*)-IDHP (Scheme 1).

Our asymmetric synthesis of (*R*)-IDHP commenced with commercially available 3,4-dihydroxybenzaldehyde **1**, which was transformed into (*E*)-isopropyl 3,4-bis(benzyloxy) cinnamate **4** by benzylation, Knoevenagel condensation, and esterification. Next, asymmetric dihydroxylation of **4** proceeded in the presence of $K_2[OsO_2(OH)_4]$ (0.2 mol %) and the chiral ligand $(QN)_2PHAL$

* Corresponding authors. Tel.: +86 29 88302686 (X.H.Z.); tel.: +86 29 84776775 (R.J.).
E-mail addresses: zhengxh@nwu.edu.cn, jiangrufmmu@yahoo.com (X. Zheng), jiangru@fmmu.edu.cn (R. Jiang).
† Co-first author.

0957-4166/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2010.11.030



Scheme 1. Synthesis of (*R*)-IDHP. Reagents and conditions: (a) BnCl, K_2CO_3, DMF, 75 °C; (b) malonic acid, 1,4-dioxane, reflux; (c) ^{i}PrOH, H_2SO_4, reflux; (d) $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, $(QN)_2PHAL$, $K_2[OsO_2(OH)_4]$, 0 °C; (e) H_2, Pd/C, HCl–^{i}PrOH, 0 °C.

(1.0 mol %) with $K_3Fe(CN)_6$ as co-oxidant, and the desired (2*R*,3*S*)-2,3-dihydroxy ester **5** was obtained in 86% yield with >99.9% ee. Next, selective deoxygenation of the 3-hydroxyl group employing 10% Pd/C catalyst in HCl–^{i}PrOH (0.5 mol L^{-1}) provided (*R*)-IDHP, while also allowing for the deprotection of phenolic hydroxyl groups.[19] Although the desired product was obtained in good yield, the enantiomeric purity was only 16.3% ee. Because almost enantioimerically pure **5** was obtained in the AD reaction, we speculated that racemization might have occurred in the last step. Therefore, we attempted to optimize the conditions for the hydrogenation of **5**.

The concentration of HCl was observed to play an important role in the reaction. The ees of the product increased as the HCl concentration dropped from 0.5 to 0.05 mol L^{-1} (Table 1, entries 1–4), and the chemical yield did not change even though the reaction time increased. Decreasing the concentration of HCl to 0.03 mol L^{-1} gave no benefit to the enantiomeric purity but lowered the chemical yield significantly (entry 5). Next, the effect of reaction temperature on the chemical yield and enantiomeric purity was also investigated, and 0 °C was found to be optimal (Table 1, entry 4). When the temperature was increased, the chemical yield increased, but the ees of the product dropped (entries 6–8). Lower temperatures resulted in a significant drop in the chemical yield (entry 9). When the reaction temperature was lowered to −20 °C, no product formed. Moreover H_2 pressure was not observed to affect neither the enantiomeric purity nor the chemical yield (entries 10 and 11). Finally, good enantiomeric purity of (*R*)-IDHP (97.8% ee) was obtained by hydrogenation of **5** in the presence of 10% Pd/C catalyst and 0.05 mol L^{-1} HCl at 0 °C under 5 bar H_2 pressure (entry 4).

Table 1
Optimization of the reaction conditions in hydrogenation of **5**

Entry	HCl (mol L^{-1})	Temperature (°C)	H_2 (bar)	Yield[a] (%)	ee[b] (%)
1	0.50	0	5	71	16.3
2	0.10	0	5	69	88.5
3	0.08	0	5	70	92.4
4	0.05	0	5	68	97.8
5	0.03	0	5	32	97.5
6	0.05	50	5	78	60.2
7	0.05	40	5	73	79.5
8	0.05	10	5	65	93.7
9	0.05	−10	5	29	97.8
10	0.05	0	4	65	97.5
11	0.05	0	6	68	97.6

[a] Yield of isolated product **5**.
[b] Determined by HPLC using a Chiracel AD column.[20]

In the same fashion, the (*S*)-enantiomer was synthesized from (*E*)-isopropyl 3,4-bis(benzyloxy) cinnamate **4** (Scheme 2). (2*S*,3*R*)-2,3-Dihydroxy ester **6** was obtained in >99.9% ee in the AD reaction adopting $(QD)_2PHAL$ as the chiral ligand. After hydrogenation, (*S*)-IDHP was prepared in 97.8% ee and 65% yield.

3. Conclusions

In summary, we have developed a novel and efficient route to (*R*)/(*S*)-IDHP starting from 3,4-dihydroxybenzaldehyde **1**. The essential stereocenters were constructed by AD reaction of (*E*)-isopropyl 3,4-bis(benzyloxy) cinnamate **4**. Convenient manipulation to both selective catalytic hydrogenation and deprotection was also accomplished in HCl–^{i}PrOH employing 10% Pd/C catalyst. The method described herein could be an attractive alternative for the synthesis of chiral α-hydroxyl esters.

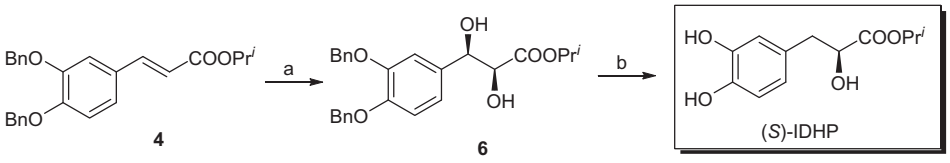
4. Experimental

4.1. General

In general, reagents and solvents were used as purchased without further purification. $K_2[OsO_2(OH)_4]$ was purchased from Aldrich Chemical Co. $(QN)_2PHAL$ and $(QD)_2PHAL$ were prepared according to literature procedures.[21] NMR spectra were recorded on Bruker Avance-400 and 500 spectrometers. High-Resolution Mass Spectroscopy (HRMS) was carried out on a BRUKER APEX-II. High performance liquid chromatography (HPLC) was performed by an Agilent 1100 interfaced to an HP 71 series computer workstation with Daicel Chiralpak AD chiral column. Optical rotations were obtained on a Perkin–Elmer 343 polarimeter.

4.2. 3,4-Dibenzyloxybenzaldehyde 2

A 500 mL three-necked round-bottomed flask was charged with 3,4-dihydroxybenzaldehyde **1** (8.30 g, 60 mmol), K_2CO_3 (41.4 g,



Scheme 2. Synthesis of (*S*)-IDHP. Reagents and conditions: (a) $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, $(QD)_2PHAL$, $K_2[OsO_2(OH)_4]$, 0 °C; (b) H_2, Pd/C, HCl–^{i}PrOH, 0 °C.

300 mmol), BnCl (17.3 mL, 150 mmol) and dry DMF (120 mL). The mixture was stirred at 75 °C until TLC indicated that **1** had disappeared. The resultant mixture was cooled to room temperature, filtered, and concentrated in vacuo. The crude oil residue was poured into water and the obtained solid was triturated, filtered, and washed with water giving 18.8 g of light yellow solid **2** (yield: 90%). Mp 90–91 °C [lit.[22] mp 88 °C].

4.3. (*E*)-3,4-Bis(benzyloxy)cinnamic acid 3

To a solution of **2** (15.0 g, 47.3 mmol) and malonic acid (14.7 g, 142.5 mmol) in 1,4-dioxane (75 mL) were added 1 mL pyridine and piperidine. Then the mixture was refluxed for 5 h. After being cooled to room temperature, the reaction mixture was poured into ice water, and concentrated HCl was added slowly until no more precipitate formed. The precipitate was collected and recrystallized from 95% EtOH to afford 14.3 g (yield: 85%) of **3** as a white solid. Mp 201–202 °C; ^{1}H NMR (500 MHz, $CDCl_3$), δ 7.67–7.63 (d, J = 15.85 Hz, 1H), 7.46–7.43 (m, 4H), 7.39–7.36 (m, 4H), 7.33–7.30 (m, 2H), 7.14–7.13 (d, J = 1.95 Hz, 1H), 7.10–7.08 (dd, J_1 = 1.9 Hz, J_2 = 2.0 Hz, 1H), 6.94–6.92 (d, J = 8.35 Hz, 1H), 6.25–6.22 (d, J = 15.85 Hz, 1H), 5.21–5.19 (d, J = 10.6 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 171.3, 151.6, 149.1, 147.0, 136.9, 136.8, 128.8, 128.1, 127.6, 127.4, 127.3, 123.5, 114.9, 114.4, 114.1, 71.5, 71.1; HRMS calcd for $C_{23}H_{20}O_4$ (M+H$^+$) 361.1395, found 361.1439.

4.4. (*E*)-Isopropyl 3,4-bis(benzyloxy) cinnamate 4

To a solution of **3** (12.0 g, 33.2 mmol) in isopropanol (200 mL) was added concentrated H_2SO_4 (4 mL) via dropping funnel. Then the solution was refluxed for 15 h. After being cooled to room temperature, satd aq $NaHCO_3$ was added and the mixture was extracted with toluene (3 × 30 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. After filtration, the solvent was removed in vacuo. The residue was purified by recrystallization (hexanes/AcOEt = 3:1) to give 2.7 g (yield: 80%) of **4** as a white solid. Mp 114–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.59–7.55 (d, J = 16 Hz, 1H), 7.49–7.45 (m, 5H), 7.41–7.35 (m, 5H), 7.14 (s, 1H), 7.10–7.08 (d, J = 8.4 Hz, 1H), 6.95–6.93 (d, J = 8.4 Hz, 1H), 6.27–6.23 (d, J = 15.6 Hz, 1H), 5.22–5.20 (d, J = 8.8 Hz, 4H), 5.16–5.11 (m, 1H), 1.33–1.32 (d, J = 6.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 166.8, 151.1, 149.1, 144.2, 137.0, 136.9, 128.7, 128.1, 128.0, 127.4, 127.3, 122.9, 116.9, 114.4, 113.8, 71.4, 71.1, 67.7, 22.1; HRMS calcd for $C_{26}H_{26}O_4$ (M+H$^+$) 403.1865, found 403.1912.

4.5. Isopropyl (2*R*,3*S*)-3-(3′,4′-bis(benzyloxy)phenyl)-2,3-dihydroxy propanoate 5

A 250 mL round-bottomed flask was charged with *tert*-butyl alcohol (36 mL), water (36 mL), $K_3Fe(CN)_6$ (5.88 g, 18.0 mmol), K_2CO_3 (2.46 g, 18.0 mmol), $CH_3SO_2NH_2$ (0.57 g, 6.0 mmol), $K_2[OsO_2(OH)_4]$ (4.5 mg, 0.012 mmol), and $(QN)_2PHAL$ (46.8 mg, 0.06 mmol). Stirring at room temperature produced two clear phases. After the solution was cooled to 0 °C, **4** (2.4 g, 6.0 mmol) was added, and the mixture was stirred vigorously at 0 °C until TLC indicated that **4** had disappeared. Na_2SO_3 (7.5 g) was added and the mixture was stirred for an additional 30 min. The mixture was extracted with AcOEt (3 × 30 mL), and then the combined organic phases were washed successively with 2 mol L^{-1} KOH (30 mL) and with H_2O (2 × 30 mL) and dried over Na_2SO_4. After the solvent was removed in vacuo, the residue was purified by column chromatography (hexane/AcOEt = 7:3) to afford 2.3 g (yield: 86%) of **5** as a white solid. Mp 107 °C. $[\alpha]_D^{25} = -2.0$ (c 1, MeOH); The ee value was >99.9%;[23] ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.49–7.45 (m, 5H), 7.41–7.36 (m, 5H), 7.09 (s, 1H); 6.93 (d, J = 8.0 Hz, 2H), 5.19–5.18 (d, J = 8.8 Hz, 4H), 5.14–5.06 (m, 1H), 4.88–4.86 (m, 1H); 4.28–4.26 (m, 1H), 3.14–3.12 (d, J = 6.0 Hz, 1H), 2.75–2.73 (d, J = 6.4 Hz, 1H), 1.28–1.26 (d, J = 6.4 Hz, 3H), 1.21–1.20 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 172.4, 149.1, 149.0, 137.4, 137.3, 133.5,128.6, 128.0,127.9, 127.6, 127.4, 119.7, 115.0, 113.7, 74.7, 74.5, 71.5, 71.4, 70.3, 21.9, 21.8; HRMS calcd for $C_{26}H_{31}NO_6$ (M+ NH_4^+) 454.2184, found 454.2228.

4.6. (*R*)-IDHP

To a solution of **5** (1.5 g, 3.44 mmol) in isopropanol (36 mL) was added HCl–^{i}PrOH (1.1 mol L^{-1}, 1.3 mL) and 10% Pd/C hydrogenation catalyst (130 mg). Under vigorous stirring, the suspension was hydrogenated at 0 °C under 5 bar H_2 pressure for 16 h. The suspension was filtered, and the clear filtrate was evaporated in vacuo. (*R*)-IDHP was obtained as brown oil in 68% yield after purification by column chromatography (hexane/AcOEt = 3:2). $[\alpha]_D^{25} = -9.72$ (c 1, MeOH). The ee value was 97.8%.[20] ^{1}H NMR (500 MHz, $CDCl_3$), δ 6.72–6.69 (m, 2H), 6.52–6.50 (d, J = 7.65 Hz, 1H), 5.32 (br, 3H), 5.03–4.98 (m, 1H), 4.31 (s, 1H), 2.95–2.91 (dd, J_1 = 3.45 Hz, J_2 = 3.30 Hz, 1H), 2.76–2.71 (dd, J_1 = 6.95 Hz, J_2 = 6.95 Hz, 1H), 1.23–1.22 (d, J = 6.25 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$), δ 174.0, 143.8, 143.1, 128.6, 121.6, 117.1, 115.6, 71.5, 69.8, 39.6, 21.8, 21.7; HRMS calcd for $C_{12}H_{16}O_5$ (M+H$^+$) 241.1031, found 241.1073.

4.7. (2*S*,3*R*)-Isopropyl-3-(3′,4′-bis(benzyloxy)phenyl)-2,3-dihydroxy propanoate 6

The preparation of **6** was carried out as described for **5**, using $(QD)_2PHAL$ as the chiral ligand in place of $(QN)_2PHAL$. The desired compound was obtained as a white powder (2.13 g, yield: 80%). Mp 107 °C. $[\alpha]_D^{25} = +2.0$ (c 1, MeOH). The ee value was >99.9%.[23]

4.8. (*S*)-IDHP

(*S*)-IDHP was prepared from **6** in 65% yield employing the same procedure as described for the preparation of (*R*)-IDHP. $[\alpha]_D^{25} = +9.7$ (c 1, MeOH). The ee value was 97.8%.[20] ^{1}H NMR (500 MHz, $CDCl_3$), δ 6.75–6.72 (m, 2H), 6.62–6.60 (d, J = 8.0 Hz, 1H), 5.90–5.70 (br, 3H), 5.09–5.04 (m, 1H), 4.37–4.35 (m, 1H), 3.02–2.98 (dd, J_1 = 4.25 Hz, J_2 = 4.25 Hz, 1H), 2.85–2.80 (dd, J_1 = 6.65 Hz, J_2 = 6.65 Hz, 1H), 1.27–1.26 (d, J = 6.25 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 143.7, 142.9, 128.5, 121.7, 116.9, 115.4, 71.5, 70.0, 21.8, 21.7.

Acknowledgments

This work was financially supported by the National Natural Science Foundation of China (Nos: 20972189, 30901883 and 81001398) and Major Program of Ministry of Science and Technology of China (No: 2009ZXJ09004-081).

References

1. Cheng, T. O. *Int. J. Cardiol.* **2006**, *113*, 437–438.
2. Lay, I. S.; Chiu, J. H.; Shiao, M. S.; Lui, W. Y.; Wu, C. W. *Planta Med.* **2003**, *69*, 26–32.
3. Makino, T.; Wakushima, H.; Okamoto, T.; Okukubo, Y.; Saito, K.; Kano, Y. *Biol. Pharm. Bull.* **2002**, *25*, 523–525.
4. Ji, X.; Tan, B. K.; Zhu, Y. C.; Linz, W.; Zhu, Y. Z. *Life Sci.* **2003**, *73*, 1413–1426.
5. Sun, J.; Huang, S. H.; Tan, B. K.; Whiteman, M.; Zhu, Y. C.; Wu, Y. J.; Ng, Y.; Duan, W.; Zhu, Y. Z. *Life Sci.* **2005**, *76*, 2849–2860.
6. Zhou, W.; Ruigrok, T. J. *Am. J. Chin. Med.* **1990**, *18*, 19–24.
7. Jang, S. I.; Jeong, S. I.; Kim, K. J.; Kim, H. J.; Yu, H. H.; Park, R.; Kim, H. M.; You, Y. O. *Planta Med.* **2003**, *69*, 1057–1059.
8. Mosaddik, M. A. *Phytomedicine* **2003**, *10*, 682–685.
9. Zheng, X. H.; Zhao, X. F.; Zhao, X.; Wang, S. X.; Wei, Y. M.; Zheng, J. B. *China patent:* CN200410026205.3.

10. Wang, S. P.; Zang, W. J.; Kong, S. S.; Yu, X. J.; Sun, L.; Zhao, X. F.; Wang, S. X.; Zheng, X. H. *Eur. J. Pharmacol.* **2008**, *579*, 283–288.
11. Tian, J. W.; Li, G. S.; Liu, Z. F.; Zhang, S. M.; Qu, G. W.; Jiang, W. L.; Fu, F. H. *Neurosci. Lett.* **2008**, *442*, 279–283.
12. Davis, F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 2402–2404.
13. Jung, J. E.; Ho, H.; Kim, H. D. *Tetrahedron Lett.* **2000**, *41*, 1793–1796.
14. Burk, M. J.; Kalberg, C. S.; Pizzano, A. *J. Am. Chem. Soc.* **1998**, *120*, 4345–4353.
15. Carpentier, J. F.; Mortreux, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1083–1099.
16. Merlani, M.; Barbakadze, V.; Amiranashvili, L.; Gogilashvili, L.; Yannakopoulou, E.; Chankvetadze, B. *Chirality* **2010**, *22*, 717–725.
17. Jagdale, A. R.; Reddy, R. S.; Sudalai, A. *Tetrahedron: Asymmetry* **2009**, *20*, 335–339.
18. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
19. Storz, T.; Dittmar, P. *Org. Process Res. Dev.* **2003**, *7*, 559–570.
20. (*R*)-IDHP: Daicel Chiralcel AD. Hexane/^{i}PrOH = 90:10. Flow rate = 1 mL min^{-1}. t_R(min) = 28.63 (major), 31.8 (minor); (*S*)-IDHP: Daicel Chiralcel AD. hexane/^{i}PrOH = 90:10. Flow rate = 1 mL min^{-1}. t_R(min) = 28.63 (minor), 31.8 (major).
21. Jiang, R.; Kuang, Y. Q.; Sun, X. L.; Zhang, S. Y. *Tetrahedron: Asymmetry* **2004**, *15*, 743–746.
22. Robert, R. *J. Chem. Soc., Perkin Trans. 1* **1984**, *7*, 1539–1545.
23. Compound **5**: Daicel Chiralcel AD. Hexane/^{i}PrOH = 90:10. Flow rate = 1 mL min^{-1}. t_R(min) = 88.7; **6**: Daicel Chiralcel AD. Hexane/^{i}PrOH = 90:10. Flow rate = 1 mL min^{-1}. t_R(min) = 61.0.