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A short synthesis of (+)-(*S*)-kurasoin B

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Abstract—A short efficient enantioselective synthesis leading directly to (+)-(*S*)-kurasoin B has been achieved in 5 steps and 25% overall yield from (2*E*)-ethyl-4-phenylbut-2-enoate using Sharpless asymmetric dihydroxylation and CH_3NO_2-assisted, or $Yb(OTf)_3$-catalyzed, regioselective C-3 coupling of indole as the key steps.
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1. Introduction

The protein farnesyltransferase (PFTase) inhibitors kurasoin A **1** and B **2** were isolated from the fermentation broth of the soil fungus, *Paecilomyces* sp. FO-3684[1] (Fig. 1). One of the reasons for interest in PFTase inhibitors is their potential anti-cancer properties. They inhibit farnesyltransferase in a dose-dependent manner. The IC_{50} values for **1** and **2** against PFTase were 59.0 and 58.7 μM, respectively.[2b] It has also been found that the stereochemistry of the hydroxyl functional group is important for eliciting PFTase inhibition.[2b] Kurasoins A and B are acyloin compounds which have in common, a 3-hydroxy-1-phenyl-2-butanone moiety, to which 4-hydroxyphenyl and 3-indolyl moieties, respectively, are connected at C-4. This feature holds potential for new lead development in that several analogues can be synthesized by modifying the aromatic substituents around the 3-hydroxy-2-butanone core unit.[3]

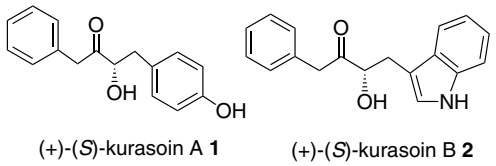

Figure 1. (+)-(*S*)-Kurasoin A and (+)-(*S*)-kurasoin B.

The structures of **1** and **2** were determined by spectroscopic analyses and synthesis of the racemates.[4] The absolute configuration was later determined by asymmetric synthesis involving the Sharpless asymmetric epoxidation.[2] The synthesis of kurasoin B[2] **2** from phenylacetaldehyde (5.7% overall yield) in 4 steps involves an intermediate in 38% yield and the coupling of indole with the chiral epoxide intermediate in a low yield of 27%. Grignard addition to a Weinreb amide leading to racemic **1** or **2** was also reported.[4] Since there was only one report on the asymmetric synthesis of **2**, it prompted the author to take up a short, high-yielding and alternative enantioselective synthesis of (+)-(*S*)-kurasoin B **2**. While this work was conceived, a new synthesis of kurasoin B **2** has appeared involving $Yb(OTf)_3$-catalyzed coupling of indole with methyl glycidate.[5]

2. Results and discussion

The Sharpless asymmetric dihydroxylation[6a–d] and subsequent conversion to epoxide function can be envisioned as powerful tools offering considerable opportunities for further synthetic manipulations.[6e,f] Herein, we report a new and short enantioselective synthesis of (+)-(*S*)-kurasoin B **2** from (2*E*)-ethyl-4-phenylbut-2-enoate **5**, employing the Sharpless asymmetric dihydroxylation as the source of chirality; conversion of the diol to an epoxide and CH_3NO_2-assisted, or $Yb(OTf)_3$-catalyzed regioselective C-3 coupling of indole as the key steps. The retrosynthetic strategy is outlined in Scheme 1.

The target compound can be prepared by regioselective C-3 indole coupling with the keto derivative of epoxide **3**,

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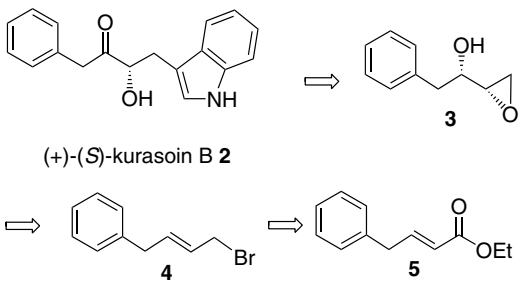
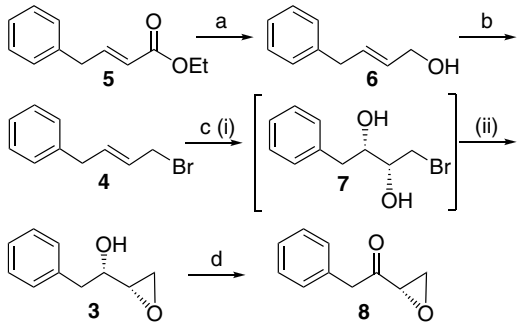


Scheme 1. Retrosynthetic analysis for (+)-(*S*)-kurasoin B **2**.

which in turn would be obtained from (2*E*)-1-bromo-4-phenylbut-2-ene **4** by asymmetric dihydroxylation. Allyl bromide **4** can be derived from the olefin ester **5**.

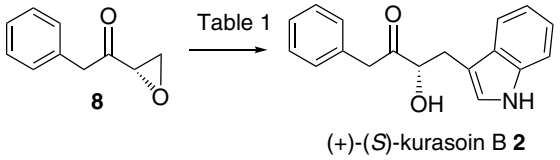
The synthesis of (+)-(*S*)-kurasoin B **2** is depicted in Scheme 2. (2*E*)-Ethyl-4-phenylbut-2-enoate **5** was easily prepared from phenylacetaldehyde by a Wittig olefination.[7] Subsequent reduction of the ester function in **5** with DIBAL-H gave the corresponding allyl alcohol **6** in 95% yield. The hydroxyl function in **6** was easily converted to the bromide using Ph_3P and NBS[8] which afforded the allyl bromide **4** in 95% yield. The Sharpless asymmetric dihydroxylation of allyl bromide **4** under standard conditions[6] and using $(DHQ)_2$-PHAL as the chiral ligand afforded the intermediate bromo-diol **7** which, without further purification, was treated with K_2CO_3 in dry MeOH to give cleanly the hydroxy-epoxide **3**[9] in 79% yield and with 95% ee.[10] Oxidation of **3** with Jones reagent [$CrO_3 + H_2SO_4$] gave the intermediate epoxy ketone **8**[2b] in 83% yield (Scheme 2).



Scheme 2. Reagents and conditions: (a) DIBAL-H (2.2 equiv), CH_2Cl_2, 0 °C, 2 h, rt, 30 min, 95%; (b) Ph_3P (1.2 equiv), NBS (1.2 equiv), CH_2Cl_2, −15 °C, 30 min, rt, 45 min, 95%; (c) (i) $K_3Fe(CN)_6$ (3.0 equiv), K_2CO_3 (3.0 equiv), $NaHCO_3$ (3.0 equiv), $MeSO_2NH_2$ (1.0 equiv), $(DHQ)_2PHAL$ (1 mol %), $K_2OsO_4{\cdot}2H_2O$ (0.4 mol %), *t*-BuOH/H_2O (1:1), 0 °C, 24 h; (ii) K_2CO_3 (2.1 equiv), MeOH, rt, 10 h, 79% over 2 steps; (d) CrO_3, H_2SO_4, acetone, rt, 30 min, 83%.

The synthesis of (+)-(*S*)-kurasoin B **2** from epoxy ketone **8** was completed as follows (Table 1). In the previous synthesis,[2] the coupling of indole with **8** was carried out in 27% yield. The reaction of the indole with epoxide **8** using $SnCl_4$ (0.3 equiv) gave only 18% of the coupled product **2** (Table 1, entry 1). When 1.2 equiv of $SnCl_4$ was employed, the coupled product **2** was obtained in 26% yield (Table 1, entry 2) similar to that reported in the literature.[2] It is known that similar reactions, carried out employing

Table 1. Coupling of indole with epoxide **8**[a]



Entry	Lewis acid (equiv)	Reaction Conditions	**2** yield (%)
1	$SnCl_4$ (0.3)	CH_2Cl_2, −5 °C, 8 h	18[b]
2	$SnCl_4$ (1.2)	CH_2Cl_2, −5 °C, 4 h	26
3	$SnCl_4$ (1.2)	CH_2Cl_2/CH_3NO_2 (4:3), −5 °C, 25 min	49
4	$Yb(OTf)_3$ (0.2)	1,2-Dichloroethane, 50 °C, 4 h	62

[a] All reactions were carried out with indole (1.5 equiv) and **8** (1 equiv).
[b] 20% of indole was recovered.

CH_3NO_2 as co-solvent, give higher yields.[11] This is attributed to the higher solubility of the intermediate Lewis acid complex with the indole or epoxide in the reaction media, thereby reducing the reaction time and increasing the yields significantly. Gratifyingly, the reaction of the indole with the epoxy ketone **8** in a mixture of CH_2Cl_2 and CH_3NO_2 (4:3) in the presence of the Lewis acid $SnCl_4$ (1.2 equiv, Table 1, entry 3) gave the C-3 coupled product **2** in a good yield of 49% {$[\alpha]_D^{20} = +30.6$ (*c* 0.2, $CHCl_3$) [lit.[2b] +31 (*c* 0.33, $CHCl_3$)]}, which is almost twice the reported yield.[2b] The same reaction, when catalyzed with $Yb(OTf)_3$[5] (Table 1, entry 4) in 1,2-dichloroethane gave **2** in 62% yield, $[\alpha]_D^{20} = +30.7$ (*c* 0.15, $CHCl_3$). The physical and spectroscopic data of **2** were in full agreement with the literature data.[2b]

3. Conclusion

In conclusion, a highly enantioselective and short synthesis of (+)-(*S*)-kurasoin B **2** from readily available (2*E*)-ethyl-4-phenylbut-2-enoate, employing the Sharpless asymmetric dihydroxylation and CH_3NO_2-assisted or $Yb(OTf)_3$-catalyzed, regioselective C-3 coupling of indole as the key steps has been achieved. The synthetic strategy involves 5 steps and gives the title compound in 25% overall yield. The method uses the Sharpless asymmetric dihydroxylation as the source of chirality to synthesize the title compound and is a good alternative to known methods.

4. Experimental

4.1. General information

Solvents were purified and dried by standard procedures before use. Commercially available reagents were used as received. Optical rotations were measured using sodium D line at 589 nm on a Perkin–Elmer, Model 343 polarimeter at 20 °C. IR spectra were recorded on Bruker TENSOR 27 spectrometer as neat thin films. ^1H NMR and ^{13}C NMR were recorded on Eclipse 300 MHz Jeol or Bruker Avance 300 MHz spectrometers with TMS at $\delta = 0.00$ ppm and

$CHCl_3$ at $\delta = 77.00$ ppm as internal standards for ^1H NMR and ^{13}C NMR, respectively. Mass spectra were recorded on Jeol AX505HA spectrometer. Elemental analyses were carried on a Carlo Erba CHNS-O analyzer.

4.2. (2*E*)-4-Phenylbut-2-ene-1-ol 6

To a stirred solution of (2*E*)-ethyl-4-phenylbut-2-enoate **5** (3.2 g, 16.82 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C under argon was added DIBAL-H (37 mL, 1.0 M in CH_2Cl_2, 37.0 mmol, 2.2 equiv) and the mixture stirred for 2 h. It was warmed to room temperature and stirred for 30 min. The mixture was quenched at 0 °C with 2 M HCl (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel using hexane/EtOAc (4:1) as eluent to give **6** (2.37 g, 95%) as a colourless oil. IR (neat): $\nu = 3358$, 3084, 3061, 3027, 2903, 2867, 1668, 1602, 1493, 1452, 1431, 1332, 1304, 1222, 1197, 1093, 1073, 1000, 971, 914, 745, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$/TMS): $\delta = 1.93$ (s, 1H, OH), 3.37 (d, $J = 6.5$ Hz, 2H, 4-H), 4.08 (dd, $J = 5.8$, 1.2 Hz, 2H, 1-H), 5.62–5.72 (m, 1H, olefin-H), 5.77–5.88 (m, 1H, olefin-H), 7.15–7.22 (m, 3H, Ph), 7.24–7.35 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$/$CHCl_3$): $\delta = 38.57$, 63.32, 126.07, 128.40 (2C), 128.50 (2C), 130.38, 131.36, 140.01. MS (EI), *m*/*z* (%): 148 [M^+] (55.5), 130 [M^+-18] (71.6), 117 (100), 115 (56.8), 92 (64.4), 91 (80.7), 78 (12.6), 57 (23.6). HRMS: [M] calcd for $C_{10}H_{12}O$, 148.0888; found, 148.0893.

4.3. (2*E*)-1-Bromo-4-phenylbut-2-ene 4

To a stirred solution of **6** (1.4 g, 9.45 mmol) in dry CH_2Cl_2 (60 mL) under argon at −15 °C was added PPh_3 (2.97 g, 11.34 mmol, 1.2 equiv) followed by NBS (2.02 g, 11.34 mmol, 1.2 equiv) and the mixture stirred for 30 min. It was then warmed to room temperature and stirred for 45 min, after which it was poured into water (50 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel using hexane/EtOAc (19:1) as eluent to give **4** (1.9 g, 95%) as colourless oil. IR (neat): $\nu = 3083$, 3061, 3028, 2962, 2902, 2836, 1659, 1602, 1494, 1452, 1432, 1328, 1263, 1205, 1135, 1074, 1029, 967, 926, 746, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$/TMS): $\delta = 3.41$ (d, $J = 6.6$ Hz, 2H, 4-H), 3.97 (dd, $J = 7.3$, 0.9 Hz, 2H, 1-H), 5.78 (ddt, $J = 15.4$, 7.6, 1.4 Hz, 1H, olefin-H), 5.87–5.98 (m, 1H, olefin-H), 7.14–7.24 (m, 3H, Ph), 7.27–7.34 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$/$CHCl_3$): $\delta = 32.87$, 38.30, 126.23, 127.53, 128.45 (2C), 128.48 (2C), 134.67, 139.21. MS (EI), *m*/*z* (%): 212 [M^+, ^{81}Br] (5.5), 210 [M^+, ^{79}Br] (5.6), 132 (12.3), 131 (100), 116 (10.4), 91 (52.7), 77 (6.7), 65 (6.8), 51 (6.2). HRMS: [M] calcd for $C_{10}H_{11}Br$, 210.0044; found, 210.0051.

4.4. (2*S*,3*S*)-1,2-Epoxy-4-phenylbutan-3-ol 3

A mixture of $K_3Fe(CN)_6$ (8.42 g, 25.58 mmol, 3.0 equiv), K_2CO_3 (3.54 g, 25.58 mmol, 3.0 equiv), $NaHCO_3$ (2.15 g, 25.58 mmol, 3.0 equiv), $MeSO_2NH_2$ (0.811 g, 8.53 mmol, 1.0 equiv), $(DHQ)_2PHAL$ (66.42 mg, 0.0853 mmol, 1 mol %), $K_2OsO_4{\cdot}2H_2O$ (12.57 mg, 0.0341 mmol, 0.4 mol %) in *t*-BuOH/H_2O (1:1, 90 mL) was stirred for 5 min at room temperature. The two phase mixture was cooled to 0 °C and the allyl bromide **4** (1.8 g, 8.53 mmol, 1.0 equiv) was added. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid Na_2SO_3 (4 g). Stirring was continued for a further 30 min and the solution extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water (2 × 50 mL), brine, dried over Na_2SO_4 and concentrated. To the residue were added dry MeOH (80 mL) and K_2CO_3 (2.48 g, 17.94 mmol, 2.1 equiv) and the mixture was stirred at room temperature for 10 h. Water (50 mL) and EtOAc (50 mL) were added. The organic layer was separated and the aqueous layer extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel using hexane/EtOAc (7:3) as eluent to give **3** (1.114 g, 79%) as a colourless oil. $[\alpha]_D^{20} = +6.42$ (*c* 1.8, $CHCl_3$) [lit.[9] +6.29 (*c* 1.080, $CHCl_3$)]. IR ($CHCl_3$): $\nu = 3419$, 3061, 3028, 3000, 2924, 1603, 1495, 1453, 1424, 1392, 1302, 1257, 1106, 1080, 1047, 990, 925, 886, 847, 746, 701, 645 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$/TMS): $\delta = 2.55$ (dd, $J = 5.0$, 3.0 Hz, 1H, 4-H), 2.71 (dd, $J = 5.0$, 4.2 Hz, 1H, 4′-H), 2.82–2.97 (m, 2H, 1-H), 2.98–3.02 (m, 1H, 2-H), 3.60–3.69 (m, 1H, 3-H), 7.20–7.24 (m, 3H, Ph), 7.26–7.32 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$/$CHCl_3$): $\delta = 40.72$, 44.98, 54.69, 72.40, 126.43, 128.35 (2C), 129.23 (2C), 137.17. MS (EI), *m*/*z* (%): 164 [M^+] (3.5), 146 (16), 133 (20.3), 118 (11.9), 103 (11.8), 92 (100), 91 (96.3), 77 (7.1), 65 (11.8), 45 (5.6). Anal. Calcd for $C_{10}H_{12}O_2$ (164.2): C 73.15; H, 7.36. Found: C 73.28; H 7.10. HRMS: [M] calcd for $C_{10}H_{12}O_2$, 164.0837; found, 164.0841. The ee was determined by converting compound **3** into the corresponding (*S*)-Mosher's ester by reaction with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenyl acetyl chloride (CH_2Cl_2/DMAP, Et_3N, 0 °C, 4 h, 88% yield). The enantiomeric purity of compound **3** was estimated to be 95%.

4.5. (2*S*)-1,2-Epoxy-4-phenylbutan-3-one 8

To a solution of **3** (1 g, 6.09 mmol) in acetone (50 mL) at room temperature was added Jones reagent (13 mL, 5.83 g of CrO_3 in 5.2 mL H_2SO_4 and 22.5 mL of H_2O) and the solution stirred for 30 min. The mixture was quenched with *iso*-propanol (2 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with water, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel using hexane/EtOAc (9:1) as eluent to give **8** (0.82 g, 83%) as a colourless oil. $[\alpha]_D^{20} = -36.4$ (*c* 1.5, $CHCl_3$) [lit.[2b] −36.0 (*c* 1.14, $CHCl_3$)]. IR (neat): $\nu = 3064$, 3031, 3005, 2923, 2854, 1720, 1621, 1603, 1584, 1497, 1454, 1399, 1369, 1318, 1271, 1246, 1178, 1127, 1111, 1071, 1029, 962, 867, 732, 714, 700, 604 cm^{-1}. ^1H NMR

(300 MHz, $CDCl_3$/TMS): $\delta = 2.86$ (dd, $J = 5.9$, 2.6 Hz, 1H, 1-H), 2.98 (dd, $J = 5.6$, 4.7 Hz, 1H, 1′-H), 3.49 (dd, $J = 4.5$, 2.4 Hz, 1H, 2-H), 3.65 (d, $J = 15.3$ Hz, 1H, 4-H), 3.75 (d, $J = 15.3$ Hz, 1H, 4′-H), 7.19–7.23 (m, 2H, Ph), 7.25–7.36 (m, 3H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$/$CHCl_3$): $\delta = 43.64$, 46.06, 53.07, 127.04, 128.31, 128.57, 129.42, 130.0, 133.51, 204.42. MS (EI), m/z (%): 162 [M^+] (13.5), 134 (4.6), 118 (24.7), 105 (13.8), 92 (14.1), 91 (100), 77 (7.5), 65 (11.9), 51 (5.6), 43 (5.5). Anal. Calcd for $C_{10}H_{10}O_2$ (162.2): C 74.05; H, 6.21. Found: C 74.18; H 6.11. HRMS: [M] calcd for $C_{10}H_{10}O_2$, 162.0681; found, 162.0687.

4.6. (*S*)-3-Hydroxy-4-(1*H*-indol-3-yl)-1-phenylbutan-2-one, (+)-kurasoin B 2 employing CH_3NO_2/CH_2Cl_2 and $SnCl_4$

To a stirred solution of indole (0.218 g, 1.86 mmol, 1.5 equiv) in CH_2Cl_2 (6 mL) under argon at −5 °C was added $SnCl_4$ (0.390 g, 0.18 mL, 1.49 mmol, 1.2 equiv) and stirred for 5 min. A solution of compound **8** (0.2 g, 1.24 mmol) in CH_3NO_2 (4.5 mL) was added and the mixture stirred for 25 min. It was then quenched with ice-water and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel using $CHCl_3$/MeOH (40:1) as eluent to give **2** (0.168 g, 49%) as a brown oil. An analytical sample was obtained by preparative TLC using $CHCl_3$/MeOH (30:1). $[\alpha]_D^{20} = +30.6$ (*c* 0.2, $CHCl_3$) [lit.[2b] +31 (*c* 0.33, $CHCl_3$)]. IR (neat): $\nu = 3400$, 3033, 3038, 2928, 2855, 1710, 1614, 1601, 1454, 1319, 1328, 1277, 1078, 1039, 912, 748, 735, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$/TMS): $\delta = 3.19$ (dd, $J = 14.3$, 7.2 Hz, 1H, 4-H), 3.35 (dd, $J = 14.3$, 4.7 Hz, 1H, 4′-H), 3.78 (d, $J = 16.0$ Hz, 1H, 1-H), 3.82 (d, $J = 16.0$ Hz, 1H, 1′-H), 4.62 (m, 1H, 3-H), 7.19–7.23 (m, 8H, Ph, indolyl), 7.41 (d, $J = 7.5$ Hz, 1H, indolyl), 7.62 (d, $J = 7.5$ Hz, 1H, indolyl). ^{13}C NMR (75 MHz, $CDCl_3$/$CHCl_3$): $\delta = 31.26$, 46.16, 77.87, 111.12, 112.41, 119.63, 119.91, 122.45, 124.77, 127.65, 127.78, 129.01, 129.41 (2C), 130.84, 135.43, 138.11, 212.71. MS (EI), m/z (%): 279 [M^+] (3.5), 261 (14.6), 160 (11.2), 149 (12.7), 130 (12.2), 119 (4.1), 91 (100), 77 (5.5), 65 (3.9), 51 (15.6), 43 (10.5). HRMS: [M] calcd for $C_{18}H_{17}NO_2$, 279.1260; found, 279.1268.

4.7. (*S*)-3-Hydroxy-4-(1*H*-indol-3-yl)-1-phenylbutan-2-one, (+)-kurasoin B 2 employing $Yb(OTf)_3$

To a stirred solution of indole (0.109 g, 0.93 mmol, 1.5 equiv) in 1,2-dichloroethane (3 mL) under argon was added $Yb(OTf)_3$ (77 mg, 0.124 mmol, 0.2 equiv) and stirred for 5 min. A solution of compound **8** (0.1 g, 0.62 mmol) in 1,2-dichloroethane (1 mL) was added and the mixture stirred at 50 °C for 4 h. It was then cooled to room temperature, quenched with ice-water and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel using $CHCl_3$/MeOH (40:1) as eluent to give **2** (0.106 g, 62%) as brown oil. Analytical sample was obtained by preparative TLC using $CHCl_3$/MeOH (30:1). $[\alpha]_D^{20} = +30.7$ (*c* 0.15, $CHCl_3$).

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