Enantioselective Synthesis of the Molluscicidal Furanosesquiterpene Lactones Ricciocarpin A and Ricciocarpin B *via* Ring Closing Metathesis

Christoph Held,[a] Roland Fröhlich,[b] Peter Metz[a,*]

[a] Institut für Organische Chemie, Technische Universität Dresden, Bergstr. 66, 01069 Dresden, Germany
Fax: (+49)-351-463-33162, e-mail: peter.metz@chemie.tu-dresden.de
[b] Organisch-Chemisches Institut, Universität Münster, Corrensstr. 40, 48149 Münster, Germany
Fax: (+49)-251-833-9772, e-mail: frohlic@nwz.uni-muenster.de

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Dedicated to Professor Hans Schäfer on the occasion of his 65th birthday

Abstract: Using two catalytic ring closing metatheses as the key events, a short, completely diastereoselective and highly enantioselective access to the molluscicidal sesquiterpenoids ricciocarpin A and ricciocarpin B was achieved. The hitherto unknown absolute configuration of these natural products is unambiguously established.

Keywords: cuprates; metathesis; natural products; structure elucidation; total synthesis

Introduction

The furanosesquiterpene lactones ricciocarpin A (**1**) and ricciocarpin B (**2**) (Figure 1) isolated from the liverwort *Ricciocarpos natans* exhibit high molluscicidal activity against the water snail *Biomphalaria glabrata*, one of the vectors of schistosomiasis (bilharziasis).[1] Though several syntheses have been published for racemic **1**,[2] none of these allows a simple transition to an enantioselective version. Moreover, no synthesis has been reported so far for the structurally similar liverwort constituent ricciocarpin B (**2**).[1] Since the absolute configuration of both **1** and **2** was unknown prior to our work, we principally wanted to devise an access to either enantiomer of these compounds. Here we give a full account on our enantioselective total synthesis of both **1** and **2**.[3]

Results and Discussion

Key element of our retrosynthetic analysis for **1** and **2** is the two-fold application of the catalytic ring closing metathesis (RCM)[4] to generate both six-membered rings of the targets (Scheme 1). As the immediate precursor for **1** we chose the cyclohexene **3** that was envisioned to be obtainable by RCM of diene **4**. Focusing on the two allylic substituents, the unsaturated δ-lactone **5** emerged as a suitable precursor. Further disconnection of this retrosynthetic intermediate by means of a second RCM transform led to acrylate **6**.

Furan-3-carboxaldehyde (**7**) has already been converted to either enantiomer of the homoallylic alcohol **8** via stoichiometric asymmetric allylborations.[5] While we could have utilized this process for our purposes, we

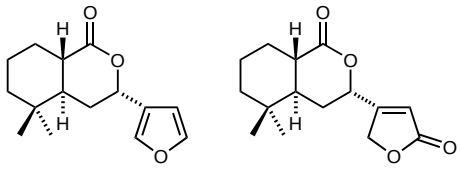
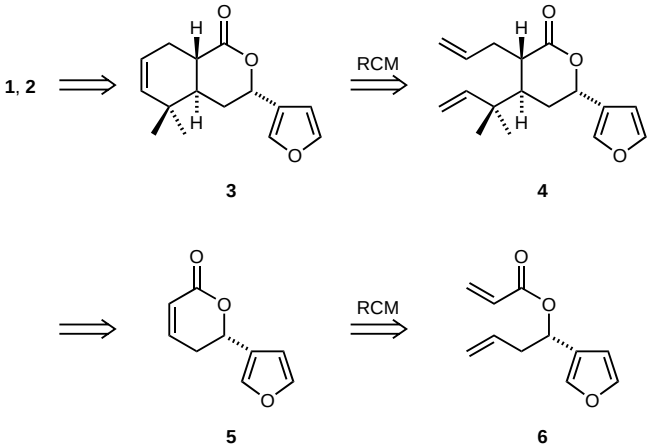


Figure 1. Sesquiterpene lactones from the liverwort *Ricciocarpos natans.*



Scheme 1. Retrosynthetic analysis.

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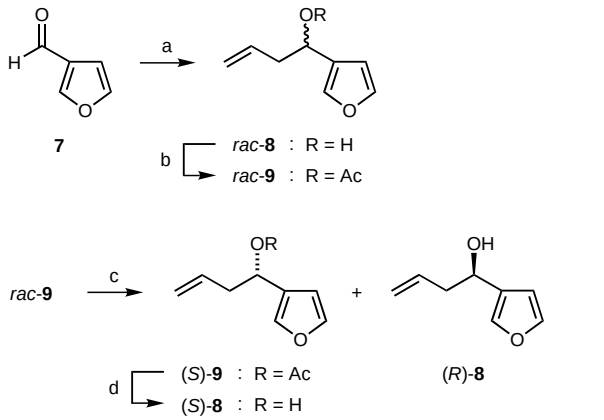
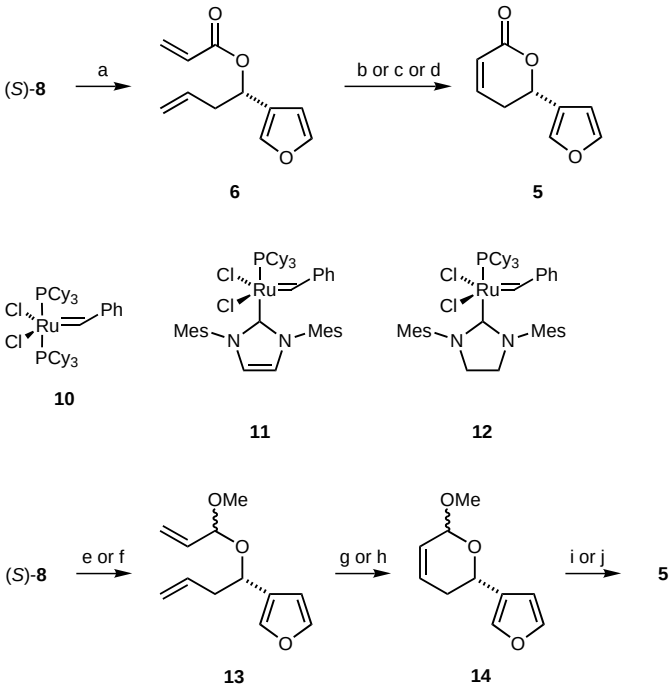


Scheme 2. a) Zn, CH_2=$CHCH_2Br$, NH_4Cl/H_2O/THF, 25 °C, 98%; b) Ac_2O, NEt_3, 10 mol % DMAP, CH_2Cl_2, 15 °C, 95%; c) lipase from *Alcaligines* sp., H_2O/DMSO, pH 7, 40 °C, 44% (*S*)-**9** (99% ee), 48% (*R*)-**8** (88% ee); d) NaOH, 25 °C, 100% (> 95% ee). DMAP = 4-dimethylaminopyridine.



Scheme 3. a) CH_2=$CHCOCl$, NEt_3, 10 mol % DMAP, CH_2Cl_2, −35 °C ® 0 °C, 83%; b) 10 mol % **10**, 30 mol % Ti(O-*i*-Pr)$_4$, CH_2Cl_2, reflux, 65%; c) 5 mol % **11**, CH_2Cl_2, reflux, 68%; d) 5 mol % **12**, CH_2Cl_2, reflux, 67%; e) CH_2=C=CHOMe, 5 mol % $Pd(OAc)_2$/dppp, NEt_3, CH_3CN, reflux, 80%; f) CH_2=C=CHOMe, 5 mol % PPTS, CH_2Cl_2, 0 °C → 25 °C, 80%; g) 10 mol % **10**, CH_2Cl_2, 25 °C, 98%; h) 0.75 mol % **10**, 0.5 mbar, 25 °C, 95%; i) 15 mol % MoO_3, H_2O_2/THF, −5 °C, then Ac_2O, NEt_3, CH_2Cl_2, 0 °C → 25 °C, 75%; j) $K_2Cr_2O_7$, H_2SO_4, acetone, 0 °C, 55%. DMAP = 4-dimethylaminopyridine, Mes = mesityl, dppp = 1,3-bis(diphenylphosphino)propane, PPTS = pyridinium *p*-toluenesulfonate.

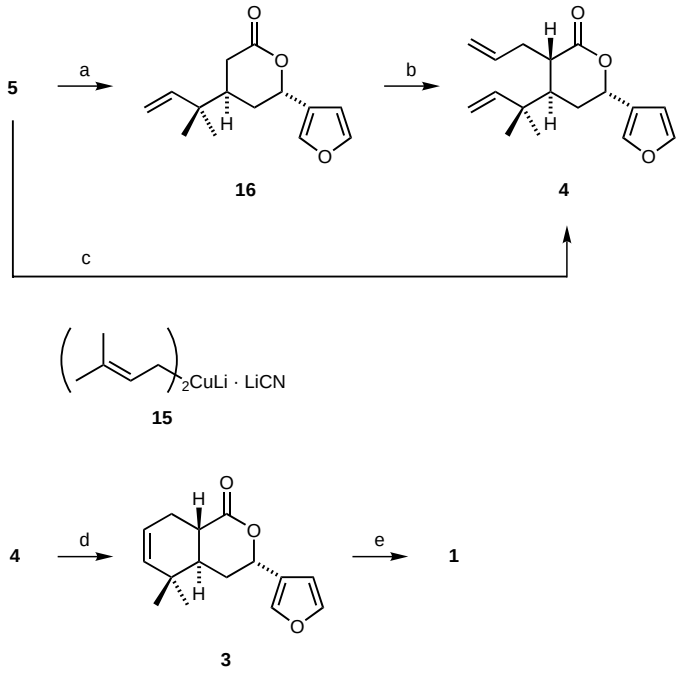
decided to develop a catalytic alternative that would be amenable to multi-gram scale-up. To this end, we screened a range of commercially available esterases and lipases for the kinetic resolution of *rac*-**8** as well as of the derived acetate *rac*-**9** (Scheme 2).[6] The alcohol *rac*-**8** was conveniently secured by a Barbier reaction of aldehyde **7** with allyl bromide and zinc.[7] Hydrolysis of *rac*-**9** catalyzed by a lipase from *Alcaligines* sp. gave the best results in terms of enantioselectivity and practicability. Next to (*R*)-**8** (88% ee by GC) this protocol provided (*S*)-**9** (99% ee by GC), which was transformed to (*S*)-**8** by alkaline hydrolysis after chromatographic separation from (*R*)-**8**. Thus, either enantiomer of **8** was at hand in gram quantities and high enantiomeric purity by asymmetric catalysis.

Alcohol (*S*)-**8** was converted to acrylate **6** with acryloyl chloride (Scheme 3). First attempts to convert **6** to lactone **5** using the Grubbs catalyst **10** or the Schrock molybdenum catalyst[8] only resulted in very low yields of the desired product. In order to reduce deactivation of catalytic intermediates by the Lewis basic carbonyl oxygen, a reagent system[9] of catalyst **10** and titanium tetraisopropoxide in the molar ratio 1:3 was applied, which improved the yield of **5** to 65%. However, the catalyst loading required was relatively high. Gratifyingly, 5 mol % of the second generation Grubbs catalysts **11** and **12**, which exhibit an enhanced reactivity towards acrylates,[10] smoothly afforded lactone **5** in 68% and 67% yield, respectively. Transition to the less Lewis basic mixed acetal **13** promised a further improvement in metathesis yield. Preparation of **13** as a 1:1 mixture of epimers at the acetal carbon succeeded in good yield by palladium-[11] or pyridinium *p*-toluenesulfonate-[12] catalyzed reaction of (*S*)-**8** with methoxyallene. While the transition metal-assisted protocol efficiently provided **13** in all runs, the yield of the PPTS catalysis proved to be rather sensitive to the exact reaction conditions. As anticipated, RCM of **13** using 10 mol % **10** resulted in an excellent yield (98%) of the dihydropyran **14** at room temperature. Nevertheless, we tried to further reduce the necessary catalyst loading. Eventually, the best results in this respect were accomplished by performing the RCM without any solvent using only 0.75 mol % **10** at reduced pressure, which guaranteed an efficient removal of the ethene produced during the metathesis. Despite the extremely high concentration, obviously no oligomerization or polymerization of the substrate occurred, and the desired heterocycle **14** was isolated in 95% yield. A chemoselective oxidation of acetal **14** to the unsaturated lactone **5** *via* molybdenum-catalyzed hydroperoxy acetal formation[13] proved to be superior to Jones oxidation[14] of **14** and completed the alternative route to this crucial intermediate.

Through two allylation reactions **5** was transformed to diene **4** (Scheme 4). First, a conjugate addition of cuprate **15**[15] to give lactone **16** took place with complete regio- and stereoselectivity as monitored by capillary GC analysis. The subsequent α-allylation of the LDA-derived lithium enolate of **16**, which yielded the

substrate **4** for the second ring closing metathesis, occurred only *trans* to the bulky dimethylallyl group. Again, no additional isomer was detected by capillary GC. Conversion of **5** to **16** could also be performed as a one-pot process by direct trapping of the intermediate enolate[16] with allyl bromide, albeit with somewhat lower yield. Diene **4** was subjected to RCM with as little as 1.7 mol % catalyst **10** at room temperature, whereupon the cyclohexene **3** was isolated in nearly quantitative yield in spite of the steric hindrance imposed by the quaternary center adjacent to one of the olefin moieties.[17] Since no reaction has been observed between 3,3-dimethylbut-1-ene and **10** under similar conditions,[18] the smooth conversion noted for **4** is surely primarily due to the intramolecular mode of attack on the sterically hindered olefin. Finally, catalytic hydrogenation of cyclohexene **3** led to (3*S*,4a*R*,8a*S*)-**1**, which proved to be identical to the naturally occurring enantiomer of ricciocarpin A by comparison of optical rotation data.[1a] Whereas the use of palladium on carbon as heterogeneous catalyst[19] turned out to be capricious due to a rather facile reduction of the furan nucleus even under 1 atm of hydrogen, homogeneous hydrogenation using the Wilkinson catalyst[20] efficiently provided **1** in a reproducible fashion.

As ricciocarpin B (**2**) only differs from **1** within the five-membered ring, we investigated different procedures for the oxidative transformation of **1** to **2** (Scheme 5). To our surprise, no conversion was observed upon treatment of **1** with *m*-chloroperbenzoic acid[21] or peracetic acid.[22] On the other hand, photooxygenation[23] of **1** was successful. After [4 + 2] cycloaddition with singlet oxygen and subsequent thermal decomposition of the primary adduct as well as reduction with sodium borohydride, a 1:1 mixture of the bislactones **2** and **17** was obtained.[23,24] By comparison of the analytical data with literature values,[1a] **2** was identified as ricciocarpin B. Moreover, X-ray diffraction analyses of **17**[3] and **2**[25] (Figure 2) were accomplished, whereby the depicted absolute configuration was proven by anomalous X-ray diffraction in both cases. These analyses also secured the configurational assignment for **8**, which so far only relied on analogy to the outcome of related allylborations[5] or on observations that some hydrolases preferentially attack a certain enantiomer in a substrate independent fashion,[26] respectively. By photooxygenation of **1** in the presence of the sterically demanding Hünig base,[27] the formation of **17** was completely suppressed, and the yield of **2** was improved to 78%.



Scheme 4. a) **15**, THF, −78 °C, then NH_4Cl/H_2O, −78 °C → 25 °C, 65%; b) LDA, THF, −78 °C, then CH_2=$CHCH_2Br$, −78 °C → 25 °C, 77%; c) **15**, THF, −78 °C → −10 °C, then CH_2=$CHCH_2Br$, −78 °C → 25 °C, 44%; d) 1.7 mol % **10**, CH_2Cl_2, 25 °C, 97%; e) 1 atm H_2, 10 mol % $RhCl(PPh_3)_3$, benzene, 25 °C, 97%. LDA = lithium diisopropylamide.

Conclusion

In summary, we have developed a short, completely diastereoselective and highly enantioselective route to the molluscicidal sesquiterpenoids ricciocarpin A (**1**) and ricciocarpin B (**2**), the absolute configuration of

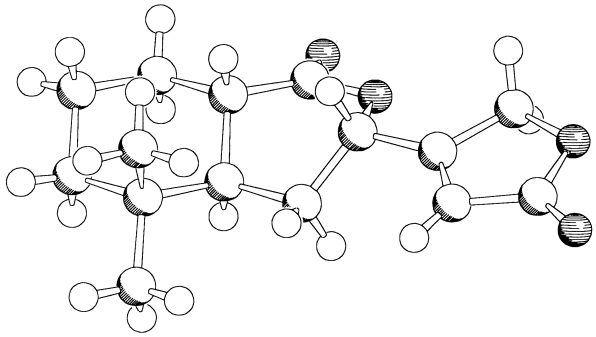
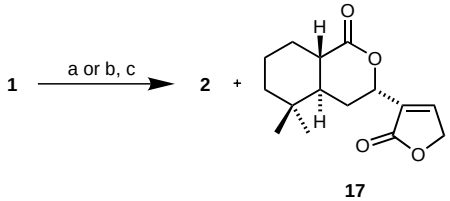


Figure 2. Crystal structure of ricciocarpin B (**2**).[25]



Scheme 5. a) 1 atm O_2, methylene blue, hv, MeOH, −40 °C, then 25 °C; b) 1 atm O_2, methylene blue, DIPEA, hv, CH_2Cl_2, −78 °C, then 25 °C; c) $NaBH_4$, MeOH, 25 °C, 25% **2** and 25% **17** from **1** *via* a) and c), 78% **2** *via* b) and c). DIPEA = diisopropylethylamine.

which was unambiguously established. Notably, neither extremely high concentration, nor steric crowding in the allylic position affected the crucial intramolecular [2 + 2] cycloaddition step of the key RCM events, which further underlines the wide applicability of this fascinating method.

Experimental Section

General Remarks

All reactions requiring exclusion of moisture were run under argon using flame-dried glassware. Solvents were dried by distillation from sodium (THF), magnesium (MeOH) or else CaH_2. The lipase from *Alcaligines* sp. (ASL) was purchased from Boehringer Mannheim. A pHstat Titroline *alpha* (Schott) was used for the kinetic enzymatic resolution of *rac*-**9**. Flash chromatography was performed on Merck silica gel 60 (40–63 μm). Capillary GC analyses were performed with a Shimadzu GC-14A or GC-14B, a Shimadzu C-R6A integrator, and an HP 5 column (25 m length, 0.25 mm i.d., 0.5 μm film). Enantiomeric excess values were determined using a Varian 3300 gas chromatograph equipped with a Macherey-Nagel chiral capillary column Hydrodex®-β-6-TBDM (50 m length, 0.25 mm i.d.). Melting points were determined on a Kofler microscope desk. Optical rotations were measured with a Perkin-Elmer 241 and a Perkin-Elmer 341 polarimeter. FT-IR spectra were obtained on a Nicolet 205; w = weak, s = strong, m = medium, br = broad. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker ASP-300 (^{1}H: 300 MHz, ^{13}C: 75.5 MHz) and a Bruker DRX-500 (^{1}H: 500 MHz, ^{13}C: 126 MHz); m_c = multiplet centered at, br = broad. ^{13}C multiplicities were determined using DEPT pulse sequences. Mass spectra (GC/MS, 70 eV) were recorded with a Hewlett Packard 5972 detector coupled with a Hewlett Packard 5890 GC. Microanalyses were performed by the analytical laboratory of the Institut für Organische Chemie, Technische Universität Dresden.

(*S*)-1-Furan-3-ylbut-3-enyl Acrylate [(*S*)-6]

A solution of acryloyl chloride (7.24 g, 80.0 mmol) in dry dichloromethane (15 mL) was added dropwise to a solution of (*S*)-**8**[3] (5.52 g, 40.0 mmol), DMAP (490 mg, 4.01 mmol) and triethylamine (16.2 g, 160 mmol) in dry dichloromethane (150 mL) cooled to −35 °C. The resultant mixture was stirred for 3 d at −35 °C and 1 d at 0 °C, treated with semi-saturated aqueous $NaHCO_3$ (100 mL) and extracted with ether (3 × 100 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification of the crude product by flash chromatography (pentane/ether, 3:2) afforded acrylate **6** as a colorless liquid; yield: 6.38 g (83%); R_f = 0.51 (pentane/ether, 7:3); $[\alpha]_D^{25}$: −63.7 (*c* 1.01, CH_2Cl_2); bp 50 °C/1.5 Pa; IR (film): $\tilde{\nu}$ = 3146 (w), 3072 (w), 2949 (w), 1720 (s, C=O), 1185 (s), 983 (m), 873 (m), 804 (s), 600 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.60 (apparent td, J_t = 7.0 Hz, J_d = 14.3 Hz, 1H), 2.66 (apparent td, J_t = 7.2 Hz, J_d = 14.1 Hz, 1H), 5.06 (d, *J* = 10.8 Hz, 1H), 5.10 (d, *J* = 17.0 Hz, 1H), 5.73 (apparent tdd, J_t = 6.9 Hz, J_d = 10.1 Hz, J_d = 17.2 Hz, 1H), 5.81 (d, *J* = 10.7 Hz, 1H), 5.90 (apparent t, *J* = 6.8 Hz, 1H), 6.10 (dd, *J* = 10.6 Hz, *J* = 17.5 Hz, 1H), 6.39 (d, *J* = 17.3 Hz, 1H), 6.40 (s, 1H), 7.36 (s, 1H) 7.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 39.13 (t), 67.92 (d), 108.91 (d), 118.20 (t), 124.37 (s), 128.49 (d), 130.87 (t), 133.02 (d), 140.36 (d), 143.17 (d), 165.40 (s); MS (GC/MS, 70 eV): *m/z* (%) = 192 (1) [M$^+$], 151 (32) [M$^+$ – C_3H_5], 120 (19) [M$^+$ – CH_2=CH-CO_2H], 95 (12), 91 (16), 55 (100) [$C_3H_3O^+$]; anal. calcd. for $C_{11}H_{12}O_3$: C 68.74, H 6.29%; found: C 68.78, H 6.48%.

(*S*)-6-Furan-3-yl-5,6-dihydropyran-2-one (5) by RCM of 6

Catalyst **11** (42 mg, 0.05 mmol) was added to a solution of acrylate **6** (192 mg, 1.00 mmol) in dry dichloromethane (25 mL). The resulting mixture was heated under reflux for 15 h and filtered through a pad of silica gel, which was eluted with ethyl acetate. After removal of the solvents under vacuum, flash chromatography (ether/triethylamine, 99:1) of the residue afforded lactone **5** as a colorless oil; yield: 112 mg (68%); R_f = 0.42 (ether); $[\alpha]_D^{25}$: −131.2 (*c* 1.06, CH_2Cl_2); bp 90 °C/2.3 Pa; IR (film): $\tilde{\nu}$ = 3140 (w), 2905 (w), 1709 (s, C=O), 1244 (s), 1020 (s), 812 (s), 783 (s), 600 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.60–2.66 (m, 2H), 5.44 (dd, *J* = 5.5 Hz, *J* = 9.9 Hz, 1H), 6.08 (d, *J* = 9.8 Hz, 1H), 6.44 (s, 1H), 6.94 (ddd, *J* = 3.3 Hz, *J* = 5.2 Hz, *J* = 9.8 Hz, 1H), 7.41 (s, 1H), 7.48 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 30.17 (t), 72.45 (d), 108.56 (d), 121.74 (d), 123.83 (s), 139.96 (d), 143.72 (d), 144.64 (d), 163.82 (s); MS (GC/MS, 70 eV): *m/z* (%) = 164 (14) [M$^+$], 95 (15) [furyl-CO$^+$], 68 (100) [$C_4H_4O^+$], 39 (58) [$C_3H_3^+$]; anal. calcd. for $C_9H_8O_3$: C 65.85, H 4.91%; found: C 65.62, H 4.94%.

(1*S*)-3-[1-(1-Methoxyallyloxy)-but-3-enyl]furan (13)

To a solution of alcohol (*S*)-**8**[3] (890 mg, 6.44 mmol) in dry acetonitrile (30 mL) was added dppp (136.5 mg, 0.33 mmol) and palladium acetate (74.1 mg, 0.33 mmol). The resulting suspension was stirred at 25 °C until a clear solution was formed. After addition of methoxyallene (2.31 g, 33.0 mmol) and triethylamine (1.00 g, 9.88 mmol), the mixture was stirred under reflux for 4.5 h. The reaction was quenched by addition of ether (30 mL), and the mixture was filtered through a pad of silica gel, which was eluted with ether. After removal of the solvents under vacuum, flash chromatography (pentane/ether, 4:1) of the residue provided acetal **13** (1:1 mixture of diastereomers) as a colorless liquid; yield: 1.07 g (80%); R_f = 0.53 (pentane/ether, 8:2); bp 50 °C/5 Pa; IR (film): $\tilde{\nu}$ = 3080 (w), 2938 (m), 2910 (s), 1503 (m), 1161 (m), 1025 (s), 936 (m), 875 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.40–2.70 (m, 2H), 3.23 and 3.24 (s, 3H), 4.50 and 4.69 (apparent t, *J* = 6.6 and 6.8 Hz, 1H), 4.79 (d, *J* = 6.1 Hz, 1H), 5.03 (d, *J* = 9.2 Hz, 1H), 5.07 (d, *J* = 16.8 Hz, 1H), 5.24–5.38 (m, 2H), 5.67–5.86 (m, 2H), 6.36 and 6.43 (s, 1H), 7.36 (s, 1H) 7.39 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 40.71 and 41.11 (t), 51.18 and 53.40 (q), 69.50 and 69.92 (d), 99.07 and 101.88 (d), 108.77 and 108.98 (d), 117.25 and 117.42 (d), 118.50 and 118.56 (t), 125.35 and 126.19 (s), 134.16 and 134.41 (d), 134.81 and 135.02 (d), 139.81 and 140.36 (d), 143.23 and 143.39 (d); MS (GC/MS, 70 eV): *m/z* (%) = 138 (4) [M$^+$ – CH_2=C=CH-OMe], 136 (1), 97 (100), [138 – $C_3H_5^+$], 95 (10), 69 (40), 41 (100) [$C_3H_5^+$]; anal. calcd. for $C_{12}H_{16}O_3$: C 69.21, H 7.74%; found: C 69.23, H 7.75%.

(2*S*)-2-Furan-3-yl-6-methoxy-3,6-dihydro-2*H*-pyran (14)

Catalyst **10** (52.7 mg, 64 μmol) was added to the neat acetal **13** (1.78 g, 8.5 mmol) at 25 °C. A strong gas evolution started immediately, continued for approximately 30 min and diminished slowly afterwards. The reaction vessel was carefully and very slowly evacuated to 0.5 mbar. After stirring for 15.5 h at room temperature and 0.5 mbar, gas evolution had completely ceased. Flash chromatography (pentane/ether/triethylamine, 79:20:1) provided **14** (1:1 mixture of diastereomers) as a colorless liquid; yield: 1.46 g (95%); $R_f = 0.31$ (pentane/ether, 8:2); bp 43 °C/1.9 Pa; IR (film): $\tilde{\nu} = 2931$ (w), 2903 (w), 2829 (w), 1729 (w) 1504 (m), 1159 (m), 1046 (s), 1027 (s), 875 (m), 601 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.15 - 2.46$ (m, 2H), 3.46 (s, 3H, isomer I), 3.50 (s, 3H, isomer II), 4.76 (dd, $J =$ 3.7 Hz, $J = 10.0$ Hz, 1H, isomer I), 4.88 (dd, $J = 3.6$ Hz, $J =$ 11.0 Hz, 1H, isomer II), 4.94 (isomer II) and 5.22 (isomer I) (br s, 1H), 5.71 (isomer I) and 5.81 (isomer II) (br d, $J = 8.9$ Hz, 1H), 6.02 – 6.10 (m, 1H), 6.44 (br s, 1H), 7.39 (isomer I) and 7.41 (isomer II) (s, 1H) 7.43 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 30.87$ and 31.08 (t), 55.09 and 55.22 (q), 61.49 and 67.22 (d), 96.10 and 98.63 (d), 108.92 (d), 125.53 and 127.83 (d), 126.44 and 125.83 (s), 128.70 and 129.00 (d), 139.33 and 139.19 (d), 143.21 and 143.05 (d); MS (GC/MS, 70 eV): *m/z* (%) = 180 (1) [M^+], 165 (1) [$M^+ -$ Me], 149 (10) [$M^+ -$ MeO], 121 (23), 91 (36), 84 (100) [$C_5H_8O^+$], 69 (86), 39 (58); anal. calcd. for $C_{10}H_{12}O_3$: C 66.65, H 6.71%; found: C 66.91, H 6.95%.

(*S*)-6-Furan-3-yl-5,6-dihydropyran-2-one (5) by Oxidation of 14

Molybdenum trioxide (77 mg, 0.54 mmol) was added to a solution of acetal **14** (678 mg, 3.76 mmol) in dry tetrahydrofuran (15 mL) at −5 °C. Hydrogen peroxide (30%, 30 mL) precooled to −10 °C was added in 3 portions to this suspension under strict control of temperature. The mixture was stirred for 1 h at −5 °C and then quenched by dilution with water (150 mL). Extraction of this mixture with ethyl acetate (5 × 50 mL), washing of the combined organic layers with brine (2 × 50 mL), drying over $MgSO_4$ and evaporation of the solvents under vacuum afforded a residue, which was immediately dissolved in dry dichloromethane (50 mL). The resulting solution was cooled to 0 °C, triethylamine (1.51 g, 14.8 mmol) and acetic anhydride (0.76 g, 7.4 mmol, dropwise during 30 min) was added, and the reaction mixture was stirred for 2 h at 25 °C. After washing with water (2 × 50 mL) and back extraction of the combined aqueous layers with ether (2 × 50 mL), the combined organic layers were washed with brine (2 × 50 mL), dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography (ether) of the residue afforded lactone **5**; yield: 460 mg (75%).

(4*R*,6*S*)-4-(1,1-Dimethylallyl)-6-furan-3-yltetrahydropyran-2-one (16)

Butyllithium (6.9 mL, 1.6 M in hexane, 11.0 mmol) was added to a solution of (tributyl)prenyltin (3.94 g, 11.0 mmol) in dry tetrahydrofuran (105 mL) at −78 °C. The resultant solution was stirred for 1 h at −78 °C, and then dry CuCN (490 mg, 5.47 mmol) was added to give a brownish suspension, which was stirred for 1 h at −78 °C. A solution of lactone **5** (600 mg, 3.66 mmol) in dry tetrahydrofuran (5 mL) was added, and stirring was continued for 1 h at −78 °C. The reaction was quenched at −78 °C by addition of a 1:1:1 mixture of saturated aqueous NH_4Cl, tetrahydrofuran and water (15 mL). After extraction with ether (5 × 50 mL), the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and evaporated under vacuum. Flash chromatography (pentane/ether, 1:1) of the residue provided **16** as colorless oil; yield: 552 mg (65%); $R_f = 0.32$ (pentane/ether, 1:1); $[\alpha]_D^{25}$: +51.6 (*c* 1.04, CH_2Cl_2); IR (film): $\tilde{\nu} = 3134$ (w), 2967 (w), 2862 (w), 1735 (s, C=O), 1158 (s), 1023 (s), 874 (s), 796 (s), 600 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 0.99$ (s, 3H), 1.00 (s, 3H), 1.86 – 1.93 (m, 2H), 2.00 – 2.08 (m, 1H), 2.30 (dd, $J = 11.5$ Hz, $J = 16.2$ Hz, 1H), 2.57 (dd, $J = 5.1$ Hz, $J = 15.8$ Hz, 1H), 5.01 (d, $J = 17.5$ Hz, 1H), 5.08 (d, $J = 10.7$ Hz, 1H), 5.36 (dd, $J = 3.8$ Hz, $J = 6.9$ Hz, 1H), 5.71 (dd, $J = 10.8$ Hz, $J = 17.4$ Hz, 1H), 6.34 (s, 1H), 7.41 (s, 1H), 7.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): $\delta = 23.33$ (q), 24.08 (q), 29.89 (t), 31.48 (t), 37.44 (d), 38.79 (s), 73.08 (d), 108.28 (d), 113.61 (t), 124.85 (s), 139.53 (d), 143.77 (d), 144.28 (d), 172.58 (s); MS (GC/MS, 70 eV); *m/z* (%) = 234 (1) [M^+], 219 (21) [$M^+ -$ Me], 164 (59) [$M^+ - C_5H_{10}$], 95 (73) [furyl-CO^+], 69 (89) [$C_5H_9^+$], 41 (100) [$C_3H_5^+$], 39 (59), 27 (20); anal. calcd. for $C_{14}H_{18}O_3$: C 71.77, H 7.74%; found: C 71.69, H 8.17%.

(3*S*,4*R*,6*S*)-3-Allyl-4-(1,1-dimethylallyl)-6-furan-3-yltetrahydropyran-2-one (4) by Allylation of 16

Lithium diisopropylamide was prepared by addition of butyllithium (1.23 mL, 1.6 M in hexane, 1.97 mmol) to a solution of diisopropylamine (200 mg, 1.97 mmol) in dry tetrahydrofuran (10 mL) at −78 °C, warming the mixture to 0 °C for 5 min and cooling to −78 °C again. This cold solution was slowly added via syringe to a solution of **16** (420 mg, 1.79 mmol) in dry tetrahydrofuran (50 mL) at −78 °C. The resultant mixture was stirred for 1 h at −78 °C, and then allyl bromide (434 mg, 3.59 mmol) was added. After stirring for 16 h at this temperature, the solution was warmed to 25 °C and stirred for 1 h at this temperature. The reaction mixture was filtered through a pad of silica gel (pretreated with ether), which was eluted with ether. Evaporation of the solvents afforded pure lactone **4** as a colorless oil; yield: 378 mg (77%); $R_f = 0.41$ (pentane/ether, 1:1); $[\alpha]_D^{25}$: +19.8 (*c* 1.19, CH_2Cl_2); IR (film): $\tilde{\nu} = 3140$ (w), 3085 (w), 2961 (w), 2918 (w), 1723 (s, C=O), 1160 (s), 1060 (s), 1022 (s), 915 (s), 875 (s), 732 (s), 600 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 1.06$ (s, 3H), 1.08 (s, 3H), 1.80 (apparent td, $J_t =$ 6.1 Hz, $J_d = 4.4$ Hz, 1H), 2.00 – 2.11 (m, 2 H), 2.39 (apparent br t, $J = 6.8$ Hz, 2H), 2.62 (apparent td, $J_t = 6.6$ Hz, $J_d = 4.3$ Hz, 1H), 4.99 – 5.08 (m, 4H), 5.47 (dd, $J = 4.1$ Hz, $J = 8.2$ Hz, 1H), 5.72 (apparent tdd, $J_t = 7.2$ Hz, $J_d = 10.0$ Hz, $J_d = 17.1$ Hz, 1H), 5.81 (dd, $J = 10.8$ Hz, $J = 17.4$ Hz, 1H), 6.37 (s, 1H), 7.40 (s, 1H), 7.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): $\delta = 24.61$ (q), 25.60 (q), 28.79 (t), 38.48 (t), 39.91 (s), 41.20 (d), 42.09 (d), 72.34 (d), 108.40 (d), 113.29 (t), 117.65 (t), 125.27 (s), 135.17 (d), 139.34 (d), 143.70 (d), 145.46 (d), 173.70 (s); MS (GC/MS, 70 eV): *m/z* (%) = 274 (1) [M^+], 259 (5) [$M^+ -$ Me], 205 (14) [$M^+ - C_5H_9$], 95 (52), 81 (49), 69 (63), 41 (100) [$C_3H_5^+$]; anal. calcd. for $C_{17}H_{22}O_3$: C 74.42, H 8.08%; found: C 74.12, H 8.24.

(3*S*,4*R*,6*S*)-3-Allyl-4-(1,1-dimethylallyl)-6-furan-3-yl-tetrahydropyran-2-one (4) *via* One-Pot Bisallylation of 5

Butyllithium (2.9 mL, 1.6 M in hexane, 4.6 mmol) was added to a solution of (tributyl)prenyltin (1.69 g, 4.69 mmol) in dry tetrahydrofuran (15 mL) at −78 °C, and the resultant solution was stirred for 1 h at −78 °C. Addition of dry CuCN (211 mg, 2.34 mmol) resulted in a suspension, which was stirred for 1 h at −78 °C. A solution of lactone **5** (250 mg, 1.56 mmol) in dry tetrahydrofuran (5 mL) was added, and the mixture was stirred for 30 min at −78 °C, warmed to −10 °C during 1 h, stirred for 30 min at this temperature and then cooled to −78 °C. After stirring for 30 min at −78 °C, allyl bromide (533 mg, 4.41 mmol) was added, and the mixture was stirred for 1 h at this temperature, warmed to 25 °C during 9.5 h and stirred for 1 h at room temperature. The reaction mixture was filtered through a pad of silica gel (pretreated with ether), which was eluted with ether. Evaporation of the solvents afforded pure lactone **4** as a colorless oil; yield: 180 mg (44%).

(3*S*,4a*R*,8a*S*)-3-Furan-3-yl-5,5-dimethyl-3,4,4a,5,8,8a-hexahydroisochromen-1-one (3)

Catalyst **10** (10.3 mg, 15 μmol) was added to a solution of diene **4** (247 mg, 0.90 mmol) in dry dichloromethane (10 mL) at 25 °C. After stirring at 25 °C for 16 h, the solvent was removed under vacuum, and the residue was purified by flash chromatography (pentane/ether, 1:1) to give **3** as a white solid; yield: 215 mg (97%); $R_f = 0.38$ (pentane/ether, 1:1); $[\alpha]_D^{25}$: +102.5 (*c* 1.01, CH_2Cl_2); mp 70–74 °C; IR (KBr): $\tilde{\nu} = 3107$ (m), 2971 (m), 2959 (w), 1720 (s, C=O), 1200 (m), 1030 (m), 789 (s), 708 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 0.98$ (s, 3H), 0.99 (s, 3H), 1.80 (ddd, $J = 5.7$ Hz, $J = 8.6$ Hz, $J = 12.2$ Hz, 1H), 1.99–2.11 (m, 2H), 2.24 (apparent tdd, $J_t = 2.4$ Hz, $J_d = 11.0$ Hz, $J_d = 18.2$ Hz, 1H), 2.44 (apparent tdd, $J_t = 5.1$ Hz, $J_d = 1.2$ Hz, $J_d = 18.2$ Hz, 1H), 2.61 (apparent dt, $J_d = 5.2$ Hz, $J_t = 11.6$ Hz, 1H), 5.34 (dd, $J = 3.9$ Hz, $J = 9.0$ Hz, 1H), 5.42 (br d, $J = 10.0$ Hz, 1H), 5.56 (ddd, $J = 2.2$ Hz, $J = 5.2$ Hz, $J = 10.0$ Hz, 1H), 6.39 (s, 1H), 7.41 (s, 1H), 7.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): $\delta = 22.12$ (q), 27.10 (t), 27.93 (q), 29.64 (t), 36.06 (s), 36.39 (d), 39.54 (d), 72.15 (d), 108.35 (d), 122.60 (d), 124.68 (s), 137.69 (d), 139.59 (d), 143.69 (d), 174.58 (s); MS (GC/MS, 70 eV): *m/z* (%) = 246 (3) [M^+], 231 (16) [M^+ – Me], 201 (21), 152 (24), 119 (26), 107 (54), 94 (100), 39 (46); anal. calcd. for $C_{15}H_{18}O_3$: C 73.15, H 7.37%; found: C 73.42, H 7.70.

Ricciocarpin A (1)

$RhCl(PPh_3)_3$ (93.4 mg, 0.10 mmol) was added to a solution of **3** (253 mg, 1.03 mmol) in dry benzene (20 mL) at 25 °C. After replacing the argon in the reaction flask by hydrogen, the reaction mixture was stirred under a hydrogen atmosphere for 16 h at 25 °C and then filtered through a pad of silica gel (pretreated with ether), which was eluted with ether. The solvents were removed under vacuum, and flash chromatography (pentane/ether, 1:1) of the residue afforded ricciocarpin A (**1**) as a white crystalline solid; yield: 247 mg (97%); $R_f = 0.34$ (pentane/ether, 1:1); $[\alpha]_D^{25}$ +18.1 (*c* 1.18, CH_2Cl_2) [natural **1** (see ref.[1a]): $[\alpha]_D^{25}$: +17.8 (*c* 1.18, CH_2Cl_2)]; mp 110 °C; IR (KBr): $\tilde{\nu} = 2955$ (m), 2938 (m), 2871 (w), 1718 (s), 1165 (m), 1026 (m), 603 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 0.91$ (s, 6H), 1.17 (apparent dt, $J_d = 4.2$ Hz, $J_t = 13.8$ Hz, 1H), 1.32 (apparent tdd, $J_t = 13.2$ Hz, $J_d = 4.0$ Hz, $J_d = 11.6$ Hz, 1H), 1.43–1.46 (m, 1H), 1.46–1.50 (m, 1H), 1.53 (ddd, $J = 6.9$ Hz, $J = 9.0$ Hz, $J = 12.7$ Hz, 1H), 1.61–1.67 (m, 1H), 1.91 (ddd, $J = 4.5$ Hz, $J = 6.9$ Hz, $J = 14.5$ Hz, 1H), 2.06 (apparent td, $J_t = 9.4$ Hz, $J_d = 14.5$ Hz, 1H), 2.16–2.21 (m, 1H), 2.40 (apparent dt, $J_d = 3.6$ Hz, $J_t = 12.1$ Hz, 1H), 5.26 (dd, $J = 4.5$ Hz, $J = 9.6$ Hz, 1H), 6.39 (s, 1H), 7.40 (s, 1H), 7.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): $\delta = 18.53$ (q), 20.97 (t), 27.20 (t), 29.68 (q), 29.83 (t), 33.69 (s), 38.92 (d), 40.44 (t), 42.34 (d), 71.68 (d), 108.51 (d), 124.81 (s), 139.60 (d), 143.62 (d), 175.18 (s); MS (GC/MS, 70 eV): *m/z* (%) = 248 (15) [M^+], 151 (69), 110 (33), 94 (100), 81 (28), 67 (16), 55 (15), 41 (15).

Conversion of Ricciocarpin A (1) to Ricciocarpin B (2) and (3*S*,4a*R*,8a*S*)-5,5-Dimethyl-3-(2-oxo-2,5-dihydrofuran-3-yl)-octahydroisochromen-1-one (17)

Methylene blue (1 mg) was added to a solution of ricciocarpin A (**1**) (50 mg, 0.2 mmol) in dry methanol (25 mL). After cooling to −40 °C, the reaction mixture was irradiated for 10 min using a 500 W halogen lamp, while a continuous flow of oxygen through the solution was maintained. Then the temperature was raised to 25 °C during 2.5 h, and sodium borohydride (120 mg, 3.17 mmol) was added. After stirring for 16 h at 25 °C, the reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL). The mixture was extracted with ethyl acetate (5 × 10 mL), and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and filtered through a pad of silica gel. The solvents were removed under vacuum, and the residue was subjected to flash chromatography (ether) to give ricciocarpin B (**2**) and the isomeric butenolide **17** as white crystalline solids; yield of **2**: 13 mg (25%), yield of **17**: 13 mg (25%).

2: $R_f = 0.20$ (ether); $[\alpha]_D^{20}$: +6.3 (*c* 0.7, CH_2Cl_2) [natural **2** (see ref.[1a]): $[\alpha]_D^{20}$: +6.3 (*c* 0.9, CH_2Cl_2)]; mp 160 °C; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.90$ (s, 3H), 0.92 (s, 3H), 1.17 (apparent dt, $J_d = 4.1$ Hz, $J_t = 13.4$ Hz, 1H), 1.24–1.40 (m, 1H), 1.43–1.55 (m, 3H), 1.61–1.68 (m, 1H), 1.93–2.04 (m, 2H), 2.13–2.18 (m, 1H), 2.36 (apparent dt, $J_d = 3.5$ Hz, $J_t = 11.8$ Hz, 1H), 4.85–4.89 (m, 2H), 5.18 (dd, $J = 6.9$ Hz, $J = 7.4$ Hz, 1 H), 6.03 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 18.45$ (q), 20.69 (t), 27.06 (t), 28.33 (t), 29.57 (q), 33.67 (s), 39.05 (d), 40.19 (t), 42.18 (d), 70.63 (t), 72.51 (d), 116.35 (d), 166.38 (s), 172.42 (s), 173.48 (s); MS (GC/MS, 70 eV): *m/z* (%) = 264 (9) [M^+], 220 (17), 180 (59), 152 (33), 110 (100), 95 (59), 81 (52), 67 (48), 55 (51), 41 (49).

17: $R_f = 0.22$ (ether); $[\alpha]_D^{25}$: −33.0 (*c* 0.6, CH_2Cl_2); mp 136 °C; IR (KBr): $\tilde{\nu} = 2964$ (m), 2935 (m), 2864 (w), 1754 (m), 1729 (s), 1183 (m), 1079 (m), 1033 (s), 839 (m), 694 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.88$ (s, 3H), 0.93 (s, 3H), 1.15 (apparent dt, $J_d = 4.1$ Hz, $J_t = 13.5$ Hz, 1 H), 1.22–1.37 (m, 1H), 1.40–1.55 (m, 3H), 1.60–1.68 (m, 1H), 1.85 (apparent td, $J_t = 9.5$ Hz, $J_d = 14.5$ Hz, 1H), 2.11–2.19 (m, 2H), 2.40 (apparent dt, $J_d = 3.4$ Hz, $J_t = 12.1$ Hz, 1H), 4.86 (br s, 2H), 5.01 (m, 1H), 7.51 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 18.40$ (q), 20.87 (t), 27.14 (t), 28.06 (t), 29.65 (q), 33.79 (s), 38.97 (d), 40.37 (t), 42.37 (d), 70.76 (t), 71.92 (d), 133.16 (s), 146.72 (d), 171.39 (s), 174.68 (s); MS (GC/MS, 70 eV): *m/z* (%) = 264 (1) [M^+], 246 (20) [M^+

$-H_2O$], 231 (19), 162 (83), 154 (56), 109 (100); anal. calcd. for $C_{15}H_{20}O_4$: C 68.16, H 7.62%; found: C 67.75, H 7.81%.

Ricciocarpin B (2) by Photooxygenation/Reduction from Ricciocarpin A (1) in the Presence of Hünig Base

Methylene blue (1 mg) and diisopropylethylamine (100 μL, 0.76 mmol) were added to a solution of ricciocarpin A (**1**) (50 mg, 0.20 mmol) in dry dichloromethane (50 mL). After stirring for 30 min at 25 °C, the mixture was cooled to −78 °C and irradiated for 10 min using a 500 W halogen lamp, while a continuous flow of oxygen through the solution was maintained. The temperature was raised to 25 °C during 2.5 h, and all volatile components of the mixture were removed under vacuum. The residue was dissolved in dry methanol (20 mL), and sodium borohydride (20 mg, 0.53 mmol) was added. After stirring for 16 h at 25 °C, the reaction was quenched by addition of hydrochloric acid (10 mL, 2 N). The mixture was stirred for 2.5 h at 25 °C and then extracted with dichloromethane (5 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography (ether/dichloromethane, 1:1) of the residue afforded ricciocarpin B (**2**) as a white crystalline solid; yield: 41.3 mg (78%).

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[25] Crystal dimensions 0.50 × 0.25 × 0.10 mm, crystal system monoclinic, space group $P2_1$ (No. 4), $a = 9.080(1)$, $b = 7.413(1)$, $c = 10.645(1)$ Å, $\beta = 110.52(1)^\circ$, $V = 671.1(1)$ Å^3, $\varrho_{calcd} = 1.308$ g cm^{-3}, $2\theta_{max} = 148.5^\circ$, $Cu_{K\alpha}$ radiation, $\lambda = 1.54178$ Å, ω/2θ scans, $T = 223(2)$ K, 1909 reflections measured, 1761 independent ($R_{int} = 0.033$), of which 1690 observed reflections [$I \geq 2\sigma(I)$], $\mu = 7.68$ cm^{-1}, absorption correction via ψ-scan data (min/max transmission 0.700/0.927), structure solution by direct methods, 175 refined parameters, hydrogen atoms calculated and refined as riding atoms, $R = 0.030$, $wR^2 = 0.083$, largest difference peak and hole 0.21/−0.13 e Å^{-3}, Flack parameter −0.22(18) [refinement of the other enantiomer: 0.78(18)]. Programs used: Express, MolEN, SHELXS-97, SHELXL-97, SCHAKAL. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge

Crystallographic Data Centre as supplementary publication no. CCDC-177965. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (+44) 1223–336–033; E-mail: deposit@ccdc.cam.ac.uk].

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