# Enantioselective Synthesis of (+)-Ricciocarpin A Using an Auxiliary Hydroxyl Group and a Diastereofacial Selectivity Based Methodology

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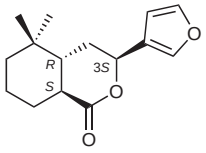
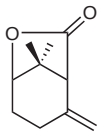
**Abstract:** An enantioselective synthesis of (+)-ricciocarpin A is described starting from (+)-karahana lactone as an enantiopure building block. This synthesis involves a stereofacially directed diastereoselective hydroboration for the installation of the required stereogenic center, and the efficient conversion of an intermediate hydroxyaldehyde to the one-carbon homologated cyanide, using the mild formation of a cyanohydrin followed by an one-pot two-step Barton–McCombie double deoxygenation sequence of the hydroxyl moieties.

**Key words:** ricciocarpin A, total synthesis, natural products, cyanohydrin, one-carbon homologation

The furanosesquiterpene lactone (+)-ricciocarpin A (**1**, Figure 1), isolated[1] from the liverwort *Ricciocarpos natans*, exhibits potent molluscicidal activity against the water snail *Biomphalaria glabrata*, a vector of schistosomiasis[2] (bilharziazis). For this reason, several racemic syntheses of ricciocarpin A have been published,[3] but none of these allows an easy transition to an enantioselective version. At this time, two enantioselective syntheses of ricciocarpin A have been published.[4] These syntheses use either a ring-closing metathesis[4a,b] or a conjugate radical addition[4c] as the key step for the construction of the six-membered rings, which are approaches quite different from our present strategy.



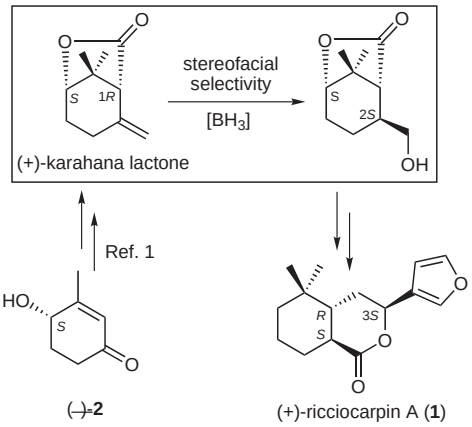
(+)-ricciocarpin A (**1**)



karahana lactone

**Figure 1**

A few years ago, we reported[5] the synthesis of both enantiomers of karahana lactone (Figure 1) and showed the utility of these enantiopure building blocks for the synthesis of natural monocyclic sesquiterpenes[6] or Taxol® A-ring subunit.[7] Based upon a related methodology, we present here the enantioselective total synthesis of the molluscicidal furanosesquiterpene (+)-ricciocarpin A (**1**) with the aid of a directing provisional hydroxyl group and a diastereofacial selectivity for the key steps. Scheme 1 shows a synopsis of this synthetic strategy.




**Scheme 1**

The starting material is (+)-karahana lactone obtained from (*S*)-4-hydroxy-3-methyl-cyclohex-2-en-1-one[5] [(–)-**2**]. The absolute stereochemistry of this alcohol controls the relative (and consequently the absolute) configuration of the newly created stereogenic centers at C-1 and then C-2. Having thus served as a control element, this auxiliary hydroxyl group is eliminated later in the synthesis without resort to specific additional steps (Scheme 2). Subjecting (+)-karahana lactone to a hydroboration–oxidation sequence using $BH_3 \cdot SMe_2$ and oxidative work up with $H_2O_2$, afforded the primary alcohol (+)-**3** as a single stereoisomer in 85% isolated yield (mp 84 °C). The stereochemistry of (+)-**3** was not proven at this stage but unequivocally established through X-ray crystallography analysis[8] carried out on the nicely crystalline TBDMS (*tert*-butyldimethylsilane) derivative (+)-**4** obtained using the standard procedure.[9] Hydride reduction of (+)-**4** with DIBAL-H (diisobutylaluminium hydride) in toluene at –78 °C gave exclusively the hydroxy aldehyde (+)-**5** in 94% yield. In keeping with our plan, elaboration of hydroxyaldehyde (+)-**5** to compound (+)-**7** next required deoxygenation of the auxiliary hydroxyl substituent and conversion of the aldehyde function to the one carbon homologated cyanide. This could be conveniently combined without resort to specific additional steps. Thus, conversion of (+)-**5** to the cyanohydrin **6** (mixture of diastereomers, 96% yield)[10] followed by Barton–McCombie

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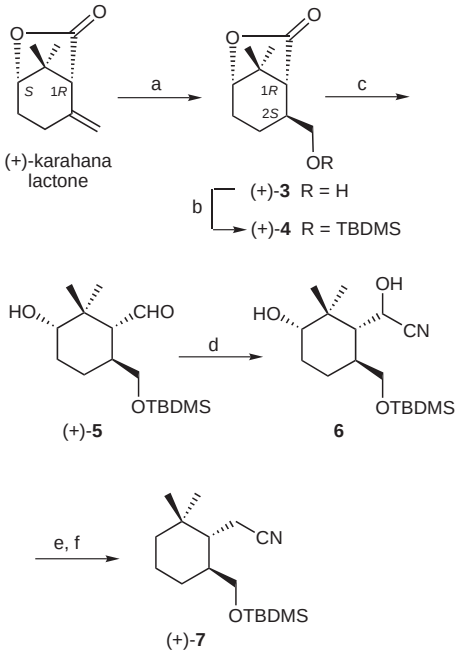
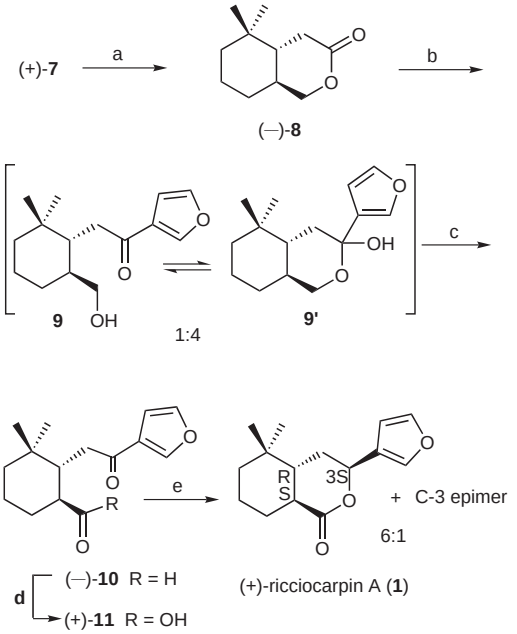



**Scheme 2** *Reagents and conditions*: a) (i) $BH_3{\cdot}SMe_2$ (1.2 equiv), THF, 3 h, r.t.; (ii) EtOH, NaOH (1.8 equiv), $H_2O_2$ (4 equiv), 1 h, r.t., 85%; b) TBSCl (1.4 equiv), imidazole (3 equiv), DMF, 3 h, r.t., 96%; c) DIBAL-H (1.3 equiv), toluene, 30 min, –78 °C, 94%; d) KCN (25 equiv), AcOH (32.5 equiv), EtOH, 12 h, r.t., 96%; e) PhOCSCl (4 equiv), DMAP (8 equiv), $CH_2Cl_2$, 12 h, r.t.; f) $Bu_3SnH$ (4 equiv), cat. AIBN, toluene, 1 h, reflux, 65% two steps.




**Scheme 3** *Reagents and conditions*: a) $TsOH{\cdot}H_2O$ (2.2 equiv), toluene, 3.5 h, reflux, 85%; b) 3-bromofuran (2.6 equiv), *n*-BuLi (2.3 equiv), $Et_2O$, 30 min, –78 °C, 84%; c) NMO (6.6 equiv), cat. TPAP, MS 4 Å, $CH_2Cl_2$, 30 min, r.t., 97%; d) $NaClO_2$ (5 equiv), $NaH_2PO_4$ (8 equiv), 2-methyl-2-butene–*t*-BuOH (1:8), 15 min, r.t., 81%; e) $NaBH_4$ (9 equiv), $CeCl_3{\cdot}7H_2O$ (2 equiv), MeOH, 12 h, –18 °C to r.t., 85%.

reaction[11] accomplished double deoxygenation to furnish the target molecule (+)-**7**[12] in 65% overall yield.

For the subsequent required lactonization of (+)-**7** (Scheme 3), a number of conditions were explored, using hydrochloric acid or *para*-toluenesulfonic acid in various solvents including methanol, THF and toluene. All of the conditions applied gave either a mixture of products or a sluggish reaction with the exception of *para*-toluenesulfonic acid (2.2 equiv) in refluxing toluene. With this combination, the reaction occurred cleanly to afford the desired δ-lactone (–)-**8**[13] exclusively in 85% yield. With the desired bicyclic lactone (–)-**8** in hand, the introduction of the furan group was addressed. For this purpose, exposure of (–)-**8** to 2.3 equivalents of 3-lithiofuran[14] in diethyl ether at –78 °C, provided a 1:4 mixture of the expected hydroxyketone **9** and the corresponding hemiketal **9′** in 84% yield. Oxidation of the so-obtained **9**/**9′** mixture with tetrapropylammonium perruthenate (TPAP)[15] delivered the ketoaldehyde (–)-**10** with high efficiency (97% yield) and oxidation of the aldehyde group with $NaClO_2$ (sodium chlorite),[16] using 2-methyl-2-butene as the chlorine scavenger,[17] provided the keto acid (+)-**11**[18] in 81% yield. Exposure of (+)-**11** to the reduction conditions described by Luche[19] gave (+)-ricciocarpin A (**1**) and the C-3 epimer as a 6:1 mixture, respectively, in 85% yield. The two diastereomers cannot be separated by column chromatography (silica gel) but they were perfectly characterized by capillary GC analysis (WCOT fused silica column; CP-Wax-52CB stationary phase). Two successive recystallizations (MeOH) afforded spectroscopically pure (+)-ricciocarpin A (**1**). The spectral and analytical characteristics of the target molecule were identical to those reported in the literature.[4,20]

In conclusion, we have proposed a highly enantioselective new route to the molluscicidal sesquiterpenoid (+)-ricciocarpin A utilizing the aid of a provisional hydroxyl group, a diastereofacial selectivity and a specific homologation sequence as the key steps. The application of this methodology to the synthesis of other furanosesquiterpenes is in progress and will be given in due course.

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(12) **Preparation and Spectroscopic Data of (+)-7.**
To a stirred solution of cyanohydrin **6** (1.41 g, 4.30 mmol) in dry $CH_2Cl_2$ (40 mL) was added at 0 °C DMAP (4.20 g, 34 mmol) and phenyl chlorothionoformate (2.40 mL, 17.2 mmol) under an argon atmosphere. After 12 h at r.t., the reaction mixture was poured into $H_2O$ and extracted with $Et_2O$. The combined organic extracts were washed with $H_2O$, dried, filtered and concentrated. To a stirred solution of the crude phenoxythiocarbonyl ester in toluene (30 mL) was added tri-*n*-butyltin hydride (4.56 mL, 17.2 mmol) and a catalytic amount of AIBN in toluene (20 mL) under an argon atmosphere. The reaction mixture was stirred under reflux for 1 h, cooled and concentrated. The resulting oily residue was purified by silica gel column chromatography to give 827 mg of pure (+)-**7** (65% yield for the two steps); $[\alpha]_D^{25}$ +19.8 (*c* 1.0, $CHCl_3$). IR (neat): ν = 2958, 2243, 1168 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 3.67 and 3.56 (ABX, *J* = 10.4, 4.2, 3.0 Hz, 2 H), 2.47 and 2.40 (ABX, *J* = 17.5, 5.1, 3.9 Hz, 2 H), 1.73–1.60 (m, 2 H), 1.53–1.32 (m, 4 H), 1.25–1.10 (m, 2 H), 0.96 (s, 3 H), 0.94 (s, 3 H), 0.87 (s, 9 H), 0.03 (s, 6 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 120.1 (C), 65.6 ($CH_2$), 44.1 (CH), 41.9 ($CH_2$), 38.9 (CH), 34.1 (C), 30.8 ($CH_3$), 30.3 ($CH_2$), 25.8 (3 × $CH_3$), 21.4 ($CH_2$), 20.2 ($CH_3$), 18.2 (C), 15.3 ($CH_2$), –5.6 (2 × $CH_3$). Anal. Calcd for $C_{17}H_{33}NOSi$: C, 69.09; H, 11.25. Found: C, 68.92; H, 11.28.
(13) **Preparation and Spectroscopic Data of (–)-8.**
A suspension of nitrile (+)-**7** (800 mg, 2.71 mmol) and *para*-toluenesulfonic acid monohydrate (1.13 g, 5.94 mmol) in toluene (20 mL) was placed in an oil bath at 120 °C. After 3.5 h, the solution was cooled to r.t. and filtered through a pad of Celite. The solvent was evaporated and a silica gel column chromatography gave 420 mg (85% yield) of (−)-**8**; $[\alpha]_D^{25}$ –33.9 (*c* 1.0, $CHCl_3$). IR (neat): ν = 2958, 1726, 1146 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 4.24 and 3.74 (ABX, *J* = 11.0, 11.0, 4.7 Hz, 2 H), 2.62 and 2.16 (ABX, *J* = 18.1, 12.4, 5.7 Hz, 2 H), 1.75–1.36 (m, 6 H), 1.32 (td, *J* = 11.5, 5.5 Hz, 1 H), 1.16 (td, *J* = 13.4, 4.3 Hz, 1 H), 0.84 (s, 3 H), 0.79 (s, 3 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 171.5 (C), 74.3 ($CH_2$), 44.6 (CH), 40.8 ($CH_2$), 32.7 (CH), 31.9 (C), 30.9 ($CH_2$), 29.1 ($CH_3$), 27.5 ($CH_2$), 20.4 ($CH_2$), 19.0 ($CH_3$). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.76; H, 9.97.
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(18) **Preparation and Spectroscopic Data of (+)-11.**
To a stirred solution of (–)-**10** (300 mg, 1.21 mmol) in a mixture of *t*-BuOH (20 mL) and 2-methyl-2-butene (2.5 mL), a solution of 80% $NaClO_2$ (683 mg, 6.04 mmol) and $NaH_2PO_4$ (1.16 g, 9.67 mmol) in $H_2O$ (10 mL) was added at r.t. The resulting mixture was stirred for 15 min then diluted with brine. The aqueous phase was saturated with NaCl and extracted thoroughly three times with EtOAc. The combined organic phases were washed with brine, dried, filtered, and concentrated. The residue was purified by silica gel column chromatography to give 260 mg (81% yield) of pure acid (+)-**11** as white crystals; mp 130 °C; $[\alpha]_D^{25}$ +7.9 (*c* 1.0, $CHCl_3$). IR (KBr): ν = 3426, 1702, 1668, 1162 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 9.58 (br s, 1 H), 8.02 (br s, 1 H), 7.39 (t, *J* = 1.8 Hz, 1 H), 6.73 (dd, *J* = 1.8, 0.6 Hz, 1 H), 2.78 and 2.64 (ABX, *J* = 17.0, 4.9, 4.4 Hz, 2 H), 2.32 (m, 2 H), 1.90 (m, 1 H), 1.65–1.25 (m, 5 H), 0.89 (s, 3 H), 0.85 (s, 3 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 194.3 (C), 181.6 (C), 146.9 (CH), 143.9 (CH), 127.6 (C), 108.7 (CH), 46.2 (CH), 42.5 (CH), 41.2 ($CH_2$), 40.9 ($CH_2$), 33.6 (C), 30.5 ($CH_3$), 30.1 ($CH_2$), 20.9 ($CH_2$), 20.0 ($CH_3$). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.89; H, 7.67.
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(20) **Preparation and Spectroscopic Data of (+)-Ricciocarpin A (1).**
A solution of (+)-**11** (160 mg, 0.60 mmol) and $CeCl_3 \cdot 7H_2O$ (450 mg, 1.21 mmol) in MeOH (20 mL) was stirred 12 h at r.t. The solution was cooled to –18 °C, $NaBH_4$ (204 mg, 5.40 mmol) was added in three portions (3 × 1 h) and the mixture was slowly allowed to rise to r.t. After 12 h, the reaction mixture was poured into ice-water, acidified (HCl 6 N, pH = 1) and stirred for 30 min at r.t. The solution was saturated with NaCl and extracted with EtOAc. The combined organic extracts were washed with brine, dried and filtered. Concentration of the filtrate followed by silica gel column chromatography gave 127 mg (85% yield) of a 6:1 mixture of (+)-**1** and the C-3 epimer. Two recrystallizations from MeOH afforded pure (+)-ricciocarpin A(**1**) as white needles; mp 109 °C [lit.[4] mp 110 °C]; $[\alpha]_D^{25}$ +17.5 (*c* 1.0, $CH_2Cl_2$). IR (KBr): ν = 2963, 1722, 1162, 1029 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.43 (br s, 1 H), 7.40 (m, 1 H), 6.39 (m, 1 H), 5.27 (dd, *J* = 9.5, 4.5 Hz, 1 H), 2.40 (td, *J* = 12.1, 3.5 Hz, 1 H), 2.24–2.14 (m, 1 H), 2.06 and 1.93 (ABMX, $J_{AB}$ = 14.5 Hz, $J_{AX} = J_{AM}$ = 9.5 Hz, $J_{BM}$ = 7.0 Hz, $J_{BX}$ = 4.5 Hz, 2 H), 1.68–1.23 (m, 5 H), 1.15 (td, *J* = 13.8, 4.3 Hz, 1 H), 0.91 (s, 6 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 175.1 (C), 143.6 (CH), 139.6 (CH), 124.8 (C), 108.5 (CH), 71.7 (CH), 42.3 (CH), 40.4 ($CH_2$), 38.9 (CH), 33.7 (C), 29.8 ($CH_2$), 29.7 ($CH_3$), 27.2 ($CH_2$), 21.0 ($CH_2$), 18.5 ($CH_3$). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.31; H, 8.09.