A SHORT SYNTHESIS OF (±)-RICCIOCARPIN A USING INTRAMOLECULAR REDUCTIVE MICHAEL REACTION

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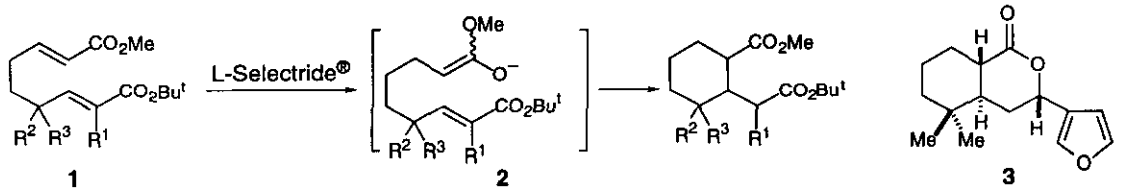
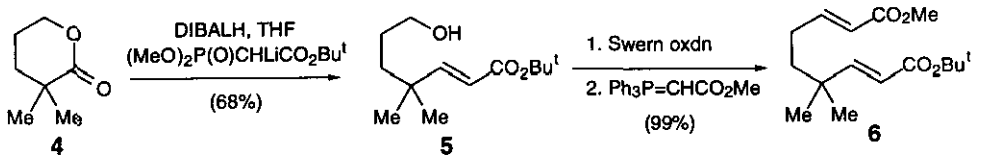
Abstract - A synthesis of furanosesquiterpene ricciocarpin A (**3**), featuring the efficient construction of the cyclohexane framework by intramolecular reductive annulation using L-Selectride®, is described.

Recently we have reported a new strategy for stereoselective construction of functionalized cyclohexane derivatives which involves intramolecular Michael reaction of enoate (**2**) derived by lithium tri-*sec*-butylborohydride (L-Selectride®) reduction of bis enoate (**1**).[1] As a part of our effort to explore the synthetic utility of the methodology, we applied to the construction of the substituted cyclohexane moiety of ricciocarpin A (**3**)[2,3] which is a furanosesquiterpene isolated from *Ricciocarpos natans* and exhibits potent molluscicidal activity.

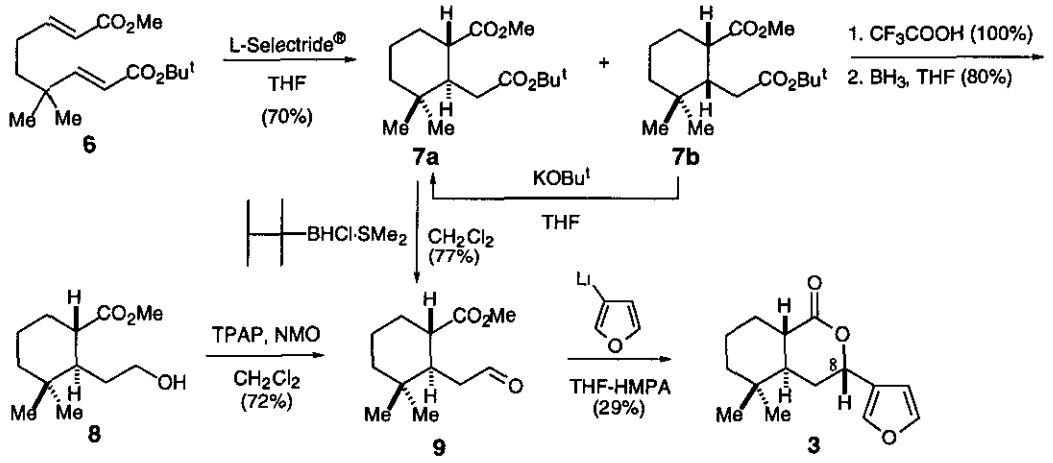


Bis enoate (**6**),[1a] a substrate of the reductive annulation, was obtained from α,α-dimethyl-δ-lactone (**4**)[4] by a three-step reaction sequence; (1) DIBALH reduction in the presence of phosphonate anion[5] (only the *E* isomer (**5**), 68%), (2) Swern oxidation of the resultant alcohol, and (3) Wittig olefination (99% overall yield).



Treatment of the bis enoate (**6**) with L-Selectride® in THF at -70 to -75 °C for 30 min and then at -25 °C for 3 h afforded *trans*- and *cis*-cyclohexanecarboxylates (**7a**,**b**) in a ratio of 79:21 (70%).[1a] The *cis* isomer (**7b**) could be equilibrated with potassium *t*-butoxide in THF to the *trans* isomer (**7a**). This product was transformed into the Eicher's aldehyde (**9**)[3a] in 58% overall yield by diborane reduction of carboxylic acid

derived by selective hydrolysis of the *t*-butyl ester with CF_3COOH, followed by tetra-*n*-propylammonium perruthenate (TPAP) oxidation of the resultant alcohol (**8**). Alternatively, and in a more direct manner, the aldehyde (**9**) was obtained in 77% yield by treatment of the ester (**7a**) with thexylchloroborane.[6] Exposure of the aldehyde (**9**) to 3-furyllithium furnished (±)-ricciocarpin A in 20% yield, together with the formation of C-8 epimer (10%). The use of HMPA as the cosolvent afforded slightly better yield (29%) of **3** with no formation of the C-8 epimer.[7] Synthetic **3** showed ^{1}H-NMR and ^{13}C-NMR spectra indistinguishable from those of natural ricciocarpin A.



EXPERIMENTAL

General: IR spectra were recorded on a Perkin-Elmer FT1640 spectrometer. ^{1}H NMR spectra were taken on Varian UnityPlus 500 (500 MHz) or Varian Gemini 300 (300 MHz) in $CDCl_3$ with reference to $CHCl_3$ (δ 7.26). ^{13}C NMR spectra were measured with Varian UnityPlus 500 (125 MHz) or Varian Gemini 300 (300 MHz) in $CDCl_3$ with reference to the $CDCl_3$ triplet (δ 77.2). Resonance patterns were described as s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad. Low-resolution mass spectra (EI-MS) were obtained with a JEOL JMS-AX-505HAD spectrometer. Liquid chromatography under medium pressures (MPLC) was carried out with a JASCO PU-980 pump system by using prepacked columns (25 mm x 450 mm, 10 μ silica gel) (Kusano Kagakukikai Co.). For routine chromatography, the following adsorbents were used: Fuji-Davison silica gel BW-200 (150-325 mesh) for column chromatography; Merck precoated silica gel 60 F-254 plates for analytical thin-layer chromatography. All moisture sensitive reactions were performed under a positive pressure of nitrogen. Anhydrous $MgSO_4$ was used for drying all organic solvent extracts in workup, and the removal of the solvents was performed with a rotary evaporator. Dry solvents and reagents were obtained by using standard procedures. Melting points (uncorrected) were determined by using a Yanagimoto micro-melting point apparatus. Elemental combustion analysis was performed at the Microanalysis Laboratory of this University.

tert-Butyl 7-Hydroxy-4,4-dimethyl-(2*E*)-heptenoate (5)

To a cooled (-80 °C) solution of *tert*-butyl dimethylphosphonoacetate (17.9 g, 79.8 mmol) in THF (300 mL) was added *n*-BuLi (1.61 M in hexane, 51 mL, 82.1 mmol). The solution was stirred at the same

temperature for 30 min before addition of a solution of the δ-lactone (**4**) (9.5 g, 74.1 mmol) in THF (150 mL). To the resulting solution was added dropwise DIBALH (0.95 M in hexane, 77 mL, 73.2 mmmol) over 1 h. The solution was allowed to warm to rt, and then stirred at rt for 12 h. After addition of $Na_2SO_4 \cdot 10H_2O$ (100 g), the mixture was stirred for 1 h, and then filtered through Celite. The filtrate was diluted with AcOEt (200 mL), and then washed successively with 10% hydrochloric acid (100 mL x 3), aqueous saturated $NaHCO_3$ solution (100 mL x 2), and saturated brine (100 mL x 2), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel, 500 g; elution with 2:1 hexane-AcOEt) to give **5** (11.5 g, 68%). a colorless oil, R_f = 0.31 (hexane:AcOEt = 2:1). IR (film) 3410, 1715, 1645 cm^{-1}. ^1H NMR δ 1.06 (6H, s, Me), 1.39-1.53 (4H, m, H-5 and H-6), 1.49 (9H, s, *t*-Bu), 2.02 (1H, br s, OH), 3.61 (2H, t, *J* = 6.4 Hz, H-7), 5.65 (1H, d, *J* = 15.9 Hz, H-2), 6.80 (1H, d, *J* = 15.9 Hz, H-3). ^{13}C NMR δ 26.5 (Me), 28.0 (C-5 or C-6), 28.3 (*t*-Bu), 36.5 (C-4), 38.4 (C-5 or C-6), 63.4 (C-7), 80.3 (*C*Me_3), 129.8 (C-2), 156.9 (C-3), 166.8 (C=O). MS *m/e* 229 (M^+ + 1), 57 (base peak).

***tert*-Butyl 8-Methoxycarbonyl-4,4-dimethyl-(2*E*,7*E*)-heptadienoate (6)**

A solution of **5** (9.10 g, 39.9 mmol) in CH_2Cl_2 (100 mL) was added at -60 ℃ and over 5 min to a solution of chloro(dimethyl)sulfonium chloride, which was prepared by dropwise addition of DMSO (6.80 mL, 7.49 g, 95.9 mmol) to a cooled (-80 ℃) solution of oxalyl chloride (4.20 mL, 6.11 g, 48.1 mmol) in CH_2Cl_2 (300 mL). After stirring at -60 ℃ for 15 min, triethylamine (28.0 mL, 20.3 g, 201 mmol) was added. The solution was allowed to warm to 0 °C, and then a solution of methoxycarbonyltriphenylphosphorane (40.0 g, 120 mmol) in CH_2Cl_2 (300 mL) was added. After stirring at rt for 15 min, the mixture was diluted with saturated brine (150 mL), and then extracted with CH_2Cl_2 (150 mL x 3). The combined organic phases were washed with saturated brine (150 mL x 3), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel 500 g; elution with 11:1 hexane-AcOEt) to give **6** (11.1 g, 99%). An analytical sample was obtained by recrystallization from EtOH-H_2O. colorless prisms, mp 39.5 °C, R_f = 0.26 (hexane:AcOEt = 9:1). IR (KBr) 1725, 1715, 1655 cm^{-1}. ^1H NMR δ 1.07 (6H, s, Me), 1.49 (9H, s, *t*-Bu), 1.50-1.54 (2H, m, H-5), 2.09-2.14 (2H, m, H-6), 3.72 (3H, s, OMe), 5.66 (1H, d, *J* = 16.0 Hz, H-2), 5.81 (1H, dt, *J* = 15.6, 1.6 Hz, H-8), 6.78 (1H, *J* = 16.0 Hz, H-3), 6.94 (1H, dt, *J* = 15.6, 6.8 Hz, H-7). ^{13}C NMR δ 26.5 (Me-4), 27.7 (C-6), 28.3 (*t*-Bu), 36.6 (C-4), 40.4 (C-5), 51.5 (OMe), 80.4 (*C*Me_3), 120.2 (C-2), 120.9 (C-8), 149.5 (C-7), 160.0 (C-3), 166.5 (C=O), 167.2 (C=O). MS *m/e* 283 (M^+ + 1), 226, 208, 180 (base peak). Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28, Found: C, 67.79; H, 9.51.

***tert*-Butyl (2-Methoxycarbonyl-6,6-dimethylcyclohexyl)acetates (7a,b)**

A 1 M THF solution of L-Selectride® (11.7 mL, 11.7 mmol) was stirred at -80 °C, and a solution of **6** (3.0 g, 11.0 mmol) in THF (11 mL) was added over 5 min. After stirring at -75 to -70 ℃ for 30 min, the reaction mixture was allowed to warm to -25 °C, and then continued stirring for 3 h at -25 ℃ before addition of MeOH (10 mL) for quenching. The mixture was treated at 0 °C with a phosphate buffer (pH 7, 10 mL), AcOEt (50 mL), and 30% H_2O_2 (10 mL), then stirred at rt for 1 h. Organic phase was separated after addition of water (25 mL) and then the organic phase was washed with saturated brine (10 mL x 2), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel, 200 g; elution with 9:1 hexane-AcOEt) to give a 79:21 mixture of **7a** and **7b** (2.08 g, 69%). The mixture was

separated by MPLC (elution with 11:1 hexane-AcOEt). The *cis* isomer (**7b**) was isomerized to the *trans* isomer (**7a**) by treatment with KOBu^t (0.2 eq) in THF (0.1 M) at rt for 2 h. Analytical samples of **7a,b** were obtained by bulb-to-bulb distillation. **7a**: colorless oil, bp 78-83 °C (bath temp)/0.2 mmHg. R_f = 0.17 (hexane:Et_2O = 11:1). IR (film) 1735 cm^{-1}. ^1H NMR δ 0.80 and 0.90 (each 3H, s, Me-6'), 1.32 (1H, ddd, J = 13.2, 13.2, 3.5 Hz), 1.38-1.58 (4H, m), 1.43 (9H, s, *t*-Bu), 1.82-1.88 (1H, m), 1.96-2.01 (2H, m, H-1 and H-1'), 2.28-2.37 (2H, m, H-1 and H-2'), 3.64 (3H, s, OMe). ^{13}C NMR δ 20.0 (Me-6'), 21.2, 28, 2 (*t*-Bu), 30.3, 30.5 (Me-6'), 33.8 (C-6'), 36.2 (C-1), 41.1, 44.0 (C-1'), 46.6 (C-2'), 51.7 (OMe), 80.2 (CMe_3), 172.8 (C=O), 176.3 (C=O). MS *m/e* 285 (M^+ + 1), 229, 211, 197 (base peak). Anal. Calcd for $C_{16}H_{26}O_4$: C, 67.57; H, 9.92, Found: C, 67.76; H, 10.07. **7b**: colorless oil, bp 77-83 °C (bath temp)/0.2 mmHg. R_f = 0.18 (hexane:Et_2O = 11:1). IR (film) 1735 cm^{-1}. ^1H NMR δ 0.86 and 1.04 (each 3H, s, Me-6'), 1.30 (1H, ddd, J = 12.9, 12.9, 4.1 Hz, H-5'), 1.36-1.49 (2H, m, H-3' and H-4'), 1.43 (9H, s, *t*-Bu), 1.55-1.67 (2H, m, H-3' and H-4'), 2.08-2.15 (1H, m, H-1), 2.29-2.36 (2H, m, H-1 and H-1'), 2.81 (1H, ddd, J = 11.6, 3.6, 3.6 Hz, H-2'), 3.65 (3H, s, OMe). ^{13}C NMR δ 20.9 (C-4'), 23.5 (C-3'), 27.1 (Me-6'), 28.2 (*t*-Bu), 28.3 (Me-6'), 33.2 (C-1), 33.8 (C-6'), 34.2 (C-5'), 42.0 (C-1'), 42.5 (C-2'), 51.6 (OMe), 80.2 (CMe_3), 173.0 (C=O), 176.2 (C=O). MS *m/e* 285 (M^+ + 1), 228, 211 (base peak).

Methyl (1*R,2*S**)-2-(2-Hydroxyethyl)-3,3-dimethylcyclohexanecarboxylate (8)**

To a cooled (ice-water) solution of **7a** (1.2 g, 4.20 mmol) in CH_2Cl_2 (12 mL) was added CF_3COOH (12 mL), and then the solution was stirred at the same temperature for 10 min. After continued stirring at rt for 1.5 h, the mixture was concentrated to give almost pure carboxylic acid (961 mg, 100%) as a colorless solid. mp 75-77 °C (Et_2O-hexane), R_f = 0.20 (hexane:AcOEt = 2:1). IR (KBr) 1730, 1705 cm^{-1}. ^1H NMR δ 0.90 (3H, s, Me-3), 0.99 (3H, s, Me-3), 1.23-1.67 (4H, m), 1.83-1.90 (1H, m), 1.97-2.13 (2H, m), 2.22-2.40 (1H, m), 2.49 (1H, dd, J = 15.9, 3.3 Hz), 3.61 (3H, s, OMe), 9.44 (1H, br s, COOH). ^{13}C NMR δ 20.3, 21.2, 30.4, 30.5, 34.0, 36.2, 41.1, 44.2, 46.9, 51.8 (OMe), 172.9 (C=O), 180.5 (C=O). MS *m/e* 228 (M^+), 147 (base peak).

To a cooled (ice-salt) solution of the carboxylic acid (950 mg, 4.20 mmol) was added dropwise BH_3·SMe_2 (0.510 mL, 5.4 mmol) over 20 min. The reaction mixture was allowed to warm to rt and then stirred for 12 h. An aqueous solution of K_2CO_3 (1 g/3 mL) was added to the mixture, and the phases were separated. The aqueous phase was extracted with Et_2O (10 mL x 3). The combined organic phases were washed with saturated brine (10 mL x 2), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel, 100 g; elution with 2:1 hexane-AcOEt) to give **8** (712 mg, 80%). a colorless oil, R_f = 0.27 (hexane:AcOEt = 2:1). IR (film) 3305 cm^{-1}. ^1H NMR δ 0.79 (3H, s, Me-3), 0.90 (3H, s, Me-3), 1.13-1.60 (8H, m), 1.69-1.85 (3H, m), 3.58 (2H, m), 3.67 (3H, s, OMe). ^{13}C NMR δ 20.2, 21.6, 30.4, 30.9, 32.6, 33.7, 36.2, 41.2, 44.6, 52.0 (OMe), 59.0 (C-2'), 175.4 (C=O). MS *m/e* 215 (M^+ + 1).

Methyl (1*R,2*S**)-3,3-Dimethyl-2-(2-oxoethyl)cyclohexanecarboxylate (9)**

A solution of **8** (710 mg, 3.30 mmol) in CH_2Cl_2 (7 mL) was stirred at 0 °C for 10 min after addition of *N*-methylmorpholine *N*-oxide (582 mg, 5.00 mmol) and molecular sieves (4A, 1.7 g). To the mixture was added TPAP (58 mg, 0.170 mmol), and the reaction mixture was allowed to warm to rt after stirring for

10 min at 0 °C. After continued stirring for 1 h, the mixture was loaded directly on a silica gel column (silica gel, 130 g; 4:1 hexane-AcOEt) and chromatographed to give **9** (505 mg, 72%). a colorless oil, R_f = 0.49 (hexane:AcOEt = 2:1). ^{1}H NMR δ 0.80 (3H, s, Me-3), 0.93 (Me-3), 1.15-1.63 (6H, m), 1.83-1.91 (1H, m), 2.41-2.49 (1H, m), 3.67 (3H, s, OMe), 9.61 (1H, s, br s, CHO). ^{13}C NMR δ 22.4, 23.8, 31.3, 31.8, 32.6, 33.5, 39.3, 44.8, 45.1, 52.0 (OMe), 177.8 (C=O), 183.2 (C=O). MS *m/e* 213 (M^+ + 1), 212, 183, 181(base peak).

Reduction of the carboxylic acid with thexylchloroborane to 9

To a cooled (ice-water) solution of the carboxylic acid (430 mg, 1.90 mmol) was added dropwise ice cold solution of thexylchloroborane (2.0 M, 2.1 mL, 4.2 mmol). The solution was allowed to warm to rt, and then stirred for 15 min. After addition of ice-water (2 mL), the mixture was stirred vigorously for 1 h. After saturation with NaCl followed by neutralization with $NaHCO_3$, the mixture was extracted with CH_2Cl_2 (10 mL x3). The combined organic phases were washed with saturated brine (5 mL x 3), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel, 50 g; elution with 3:1 hexane-AcOEt) to give **9** (309 mg, 77%)

Ricciocarpin A (3)

To a cooled (-80 °C) solution of 3-bromofuran (51 μL, 0.57 mmol) in THF (2.5 mL) was added *n*-BuLi (1.61 M in hexane, 0.35 mL, 0.57 mmol), and the mixture was stirred at the same temperature for 30 min before addition of HMPA (0.40 mL) and a solution of **9** (100 mg, 0.47 mmol) in THF (1 mL). After stirring at -80 °C for 6 h, the mixture was allowed to warm to rt before addition of saturated aqueous $(NH_4)_2SO_4$ solution (4 mL). The reaction mixture was stirred at rt for 12 h, and then extracted with Et_2O (5 mL x 3). The combined organic phases were washed with saturated brine (5 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel, 15 g; elution with 3:1 hexane-Et_2O) to give **3** (34 mg, 29%) as a white solid. An analytical sample was obtained by recrystallization from Et_2O-*i*-PrOH. colorless prisms, mp 95-96 °C. R_f = 0.21 (hexane:Et_2O = 2:1). IR (KBr) 3115, 2930, 1715 cm^{-1}. ^{1}H NMR δ 0.92 (6H, s, Me-5), 1.19 (1H, ddd, *J* = 13.8, 13.8, 4.2 Hz, H-4), 1.33 (1H, dddd, *J* = 13.2, 13.2, 12.2, 4.1 Hz, H-2), 1.46 (1H, br dm, H-4), 1.49-1.58 (2H, m, H-3 and H-6), 1.64-1.69 (1H, m, H-3), 1.92 (1H, ddd, *J* = 14.4, 6.8, 4.6 Hz, H-7), 2.06 (1H, ddd, *J* = 14.4, 9.6, 9.6 Hz, H-7), 2.19 (1H, br dm, H-2), 2.42 (1H, ddd, *J* = 12.2, 12.2, 3.4 Hz, H-1), 5.27 (1H, dd, *J* = 9.6, 4.6 Hz, H-8), 6.41 (1H, m, H-10), 7.42 (1H, m, H-11), 7.45 (1H, m, H-12). ^{13}C NMR δ 18.7 and 30.0 (C-13 and C-14), 21.2 (C-3), 27.4 (C-2), 29.9 (C-7), 33.9 (C-5), 39.1 (C-1), 40.6 (C-4), 42.5 (C-6), 71.9 (C-8), 108.7 (C-10), 125.0 (C-9), 139.8 (C-11), 143.8 (C-12), 175.4 (C-15). MS *m/e* 248 (M^+), 151 (base peak), 110, 94, 81. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12, Found: C, 72.32; H, 8.39.

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7. Any identifiable product other than ricciocarpin A (**3**) was not isolated.

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