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Synthesis of Cryptocaryalactone, a 1,3-Polyol-Derived Unsaturated Lactone

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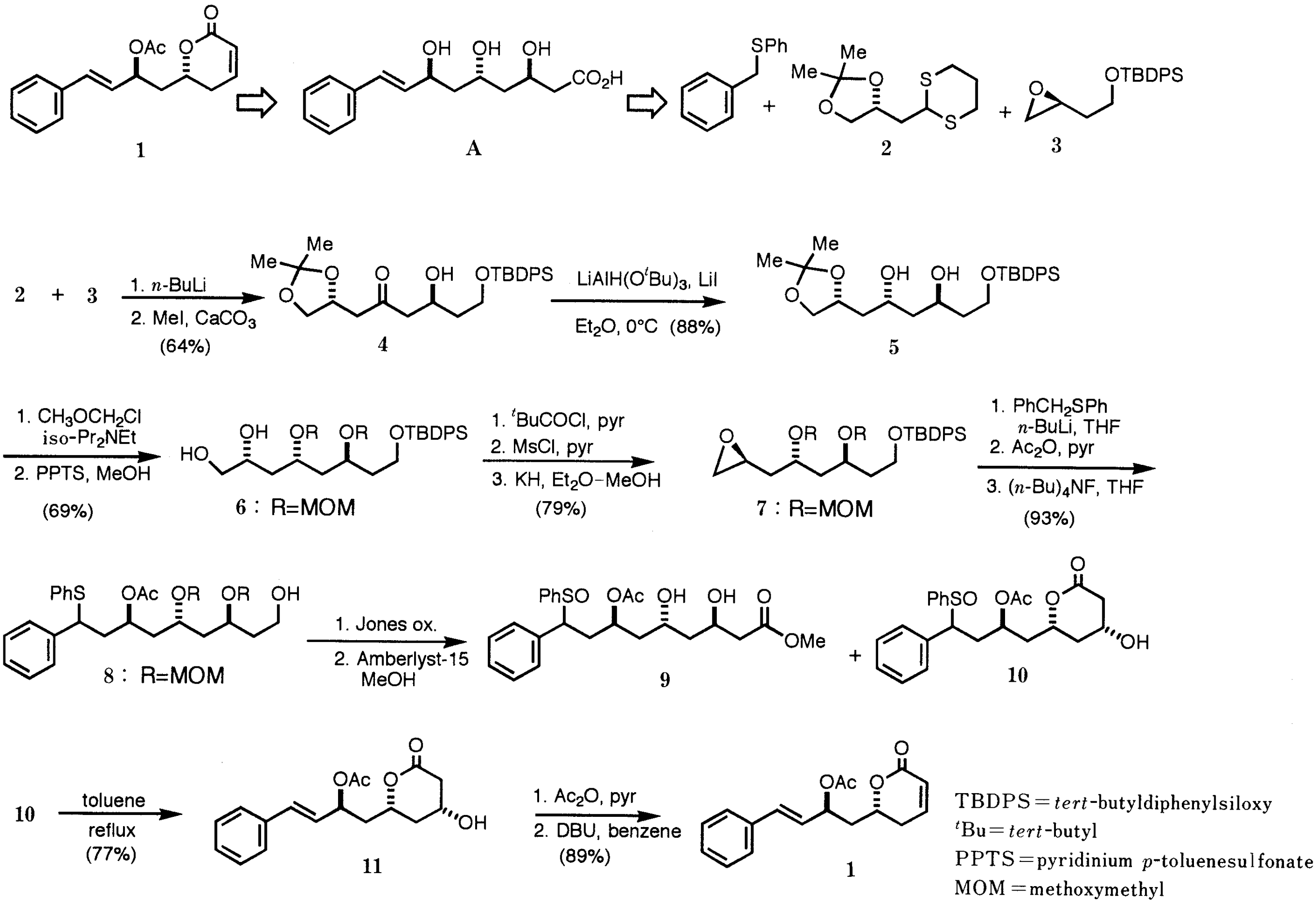
Cryptocaryalactone, a 1,3-polyol-derived α,β-unsaturated δ-lactone, has been synthesized in a stereocontrolled manner *via* the coupling reaction of a chiral dithiane with an epoxide and *anti*-stereoselective 1,3-asymmetric reduction of the derived hydroxy ketone.

Keywords 1,3-polyol; cryptocaryalactone; *Cryptocarya bourdilloni*; Lauraceae; synthesis

Higher plants produce several α,β-unsaturated δ-lactones,[1] which seem to originate biogenetically from the corresponding 1,3-polyhydroxylated acids and belong to a group of polyketides. One of the members of this group is cryptocaryalactone (**1**), which was isolated from *Cryptocarya bourdilloni* Gamb. (Lauraceae)[2,3] and whose absolute stereochemistry was established by synthesis.[4] We recently developed a method for the preparation of *anti*-1,3-polyols using a four-carbon chain extension methodology.[5] The method was stereoselective and iterative and led to the synthesis of various stereoisomers of 1,2,4,6,8-pentol derivatives.[6] We report here a stereoselective synthesis of cryptocaryalactone (**1**) based on this method.

A key feature of our method is a stereocontrolled formation of the optically active (3*R*,5*R*,7*S*)-trihydroxy acid derivative (A) or its equivalent, which could be prepared from two four-carbon units (**2**, **3**) and one benzyl unit. The coupling reaction of the optically active lithiodithiane of **2** (prepared by treatment of **2**[7] with *n*-butyllithium in tetrahydrofuran (THF) at −30 °C for 2 h) with the epoxide **3**[7] gave the adduct, which was converted to the hydroxy ketone **4** in 64% overall yield after hydrolysis with MeI–$CaCO_3$ in aqueous acetonitrile. An



TBDPS = *tert*-butyldiphenylsiloxy
${}^tBu$ = *tert*-butyl
PPTS = pyridinium *p*-toluenesulfonate
MOM = methoxymethyl

Chart 1

anti-selective 1,3-asymmetric reduction of **4** was carried out using LiAlH(O^{t}Bu)$_3$–LiI[5] to provide the *anti*-diol **5** in 88% yield after chromatographic separation of the 95 : 5 mixture of two diastereoisomers. After protection of the diol with a methoxymethyl group and deprotection of the acetonide group, giving **6** in 69% yield, the terminal 1,2-diol moiety of **6** was transformed to the β-epoxide **7** by inverting the chiral center at C-2 in 79% overall yield. Although the epoxide **7** could also be prepared by the coupling of the epoxide **3** and the enantiomer of **2**, using the same protocol described above, the 1,3-*anti* reduction with LiAlH(O^{t}Bu)$_3$–LiI and Me$_4$NBH(OAc)$_3$[8] of the resulting hydroxy ketone, a C-2 epimer of **4**, proceeded with only moderate selectivity (<85 : 15). This approach was abandoned when it became clear that the selectivity of the reduction could not be improved.

Second coupling of the epoxide **7** with the anion of benzyl phenyl sulfide (prepared by reaction with *n*-BuLi), followed by acetylation and desilylation gave **8** in 94% overall yield. Treatment of **8** with Jones reagent resulted in the oxidation of hydroxyl and phenyl sulfide groups to carboxylic acid and sulfoxide, respectively, and the product was treated with Amberlyst-15 in methanol to give a methyl ester **9** (46%) and a lactone **10** (24%). Lactonization of **9** to **10** was achieved by treatment with camphorsulfonic acid in methylene chloride in 41% yield (96% yield based on the consumed starting material). Completion of the synthesis required three more steps. Heating the sulfoxide **10** in toluene gave the lactone **11** having a *trans* olefin as a single stereoisomer in 77% yield, and this was acetylated and then treated with 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) in benzene to yield cryptocaryalactone (**1**) in 89% yield, mp 125—126 °C, $[\alpha]_D^{25}$ +18.0° (c=0.25, CHCl$_3$), lit.,[1]: mp 124—126 °C, $[\alpha]_D^{25}$ +15.55° (c=2.52, CHCl$_3$). The spectroscopic data (^{1}H-NMR, IR, MS) were identical with the reported values.[2,4] In conclusion, the stereoselective synthesis of cryptocaryalactone has been accomplished by applying a new methodology for *anti*-1,3-polyol synthesis originally developed by us.

Experimental

Optical rotations were measured on a JASCO DIP-370 polarimeter. IR spectra were taken on a Hitachi 215 spectrometer. ^{1}H-NMR spectra were measured on JEOL GX-400 and 270 spectrometers with tetramethylsilane as an internal standard. Mass spectra were taken on Shimadzu QP-1000 and Hitachi M-80 spectrometers. Flash chromatography was performed with Silica gel 60 (230—400 mesh). All organic extracts were dried over MgSO$_4$ and, after filtration, were concentrated to dryness under reduced pressure on a rotary evaporator at or below 40 °C.

(2*R*,6*S*)-8-(*tert*-Butyldiphenylsiloxy)-1,2-(isopropylidenedioxy)octan-4-one (4) A stirred solution of **2** (550 mg, 2.35 mmol) in 5 ml of dry THF under argon was treated with 2 ml of 1.6 M *n*-BuLi in hexane at −30 °C for 2 h and then a solution of **3** (590 mg, 1.8 mmol) in 2 ml of THF was added. The reaction mixture was stored at −20 °C for 28 h. The reaction was quenched with aqueous NH$_4$Cl and the mixture was extracted with ether. The extract was washed with water and brine, dried, and evaporated. Flash chromatography of the residue with 15% ethyl acetate (EtOAc) in hexane gave the adduct (804 mg, 80% yield). A mixture of the adduct (804 mg, 1.44 mmol), CaCO$_3$ (1.44 g, 14.4 mmol), and MeI (8.9 ml, 144 mmol) in 80% aqueous MeCN (80 ml) was stirred at room temperature for 24 h. The mixture was filtered through a short column of Celite using EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography (25% EtOAc–hexane) to give **4** (539 mg, 80% yield) as a colorless oil. $[\alpha]_D^{25}$ +5.63° (c=0.54, CHCl$_3$). IR (CHCl$_3$): 3500, 1705, 1110, 820 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 1.05 (9H, s, *tert*-Bu), 1.35, 1.41 (each 3H, s, 2 × Me), 1.70 (2H m), 2.56—2.72 (3H), 2.91 (1H, dd, J=16.8, 6.4 Hz), 3.45 (1H, d, J=2.7 Hz, OH), 3.55 (1H, dd, J=8.4, 6.7 Hz), 3.84 (2H, m), 4.18 (1H, dd, J=8.4, 6.1 Hz), 4.36 (1H, m), 4.48 (1H, quint, J=6.4 Hz), 7.42 (6H, m), 7.67 (4H, m). CI-MS m/z: 488 (MNH$_4^+$), 471 (MH$^+$).

(2*R*,4*R*,6*S*)-8-(*tert*-Butyldiphenylsiloxy)-1,2-(isopropylidenedioxy)-octan-4,6-diol (5) A solution of **4** (437 mg, 1.0 mmol) and LiI (1.3 g, 10 mmol) in 35 ml of dry ether was cooled to 0 °C, LiAlH(O^{t}Bu)$_3$ (1.27 g, 5 mmol) was added, and the reaction mixture was stirred for 45 min at 0 °C. After dilution with ether the mixture was quenched with 2 N KOH. The ethereal layer was separated and evaporated. The residue was flash-chromatographed with 3% acetone in CHCl$_3$ to give **5** (402 mg, 88% yield) as a colorless oil. $[\alpha]_D^{25}$ +3.64° (c=1.43, CHCl$_3$). IR (CHCl$_3$): 3500, 1425, 1110, 820 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 1.15 (9H, s, *tert*-Bu), 1.25, 1.32 (each 3H, s, 2 × Me), 1.27 (1H, ddd, J=14.2, 3.9, 3.1 Hz), 1.53 (3H, m), 1.62 (1H, dt, J=14.2, 9.0 Hz), 1.80 (1H, m), 3.30 (1H, t, J=7.8 Hz), 3.39, 3.41 (each 1H, br s, 2 × OH), 3.75 (1H, dd, J=7.8, 5.8 Hz), 3.84 (1H, ddd, J=10.5, 7.3, 5.1 Hz), 3.89 (1H, dt J=10.5, 5.4 Hz), 4.00 (1H, m), 4.26 (1H, m), 7.32 (6H, m), 7.77 (4H, m). CI-MS (NH$_3$) m/z: 473 (MH$^+$).

(2*R*,4*R*,6*S*)-8-(*tert*-Butyldiphenylsiloxy)-4,6-bis(methoxymethoxy)-octan-1,2-diol (6) A solution of **5** (640 mg, 1.36 mmol) in CH$_2$Cl$_2$ (15 ml) was treated with iso-Pr$_2$NEt (1.19 ml, 6.8 mmol) and CH$_3$OCH$_2$Cl (0.41 ml, 5.44 mmol). The mixture was stirred for 16 h and extracted with EtOAc. The extract was washed with water, 10% citric acid, saturated NaHCO$_3$, and brine successively, dried, and evaporated. Flash chromatography with 20% EtOAc in hexane gave the product (617 mg, 82% yield). This product was dissolved in methanol (12 ml) and pyridinium *p*-toluenesulfonate (12 mg) was added. The solution was heated at 40 °C for 3.5 h and then concentrated to dryness after addition of Et$_3$N (0.2 ml). Flash chromatography with 5% hexane in EtOAc gave **6** (482 mg, 84% yield). $[\alpha]_D^{25}$ +0.56° (c=0.7, CHCl$_3$). IR (CHCl$_3$): 3450, 1425, 1110, 1030 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 1.05 (9H, s, *tert*-Bu), 1.73 (6H, m), 3.34, 3.38 (each 3H, s, 2 × OMe), 3.47 (1H, dd, J=11.1, 6.7 Hz), 3.59 (1H, dd, J=11.1, 3.4 Hz), 3.74 (2H, t, J=5.4 Hz), 3.90 (3H, m), 4.61, 4.64 (each 1H, d, J=6.7 Hz, OCH$_2$O), 4.67, 4.73 (each 1H, d, J=6.7 Hz, OCH$_2$O), 7.41 (6H, m), 7.65 (4H, m).

(2*S*,4*R*,6*S*)-8-(*tert*-Butyldiphenylsiloxy)-4,6-bis(methoxymethoxy)-1,2-epoxyoctane (7) A solution of **6** (478 mg, 0.88 mmol) and *tert*-BuCOCl (0.22 ml, 1.77 mmol) in pyridine (6 ml) was stirred at 0 °C for 1 h and the reaction was quenched with MeOH (1 ml). After evaporation of the solvent the residue was purified by flash chromatography with 30% EtOAc in hexane to give the pivalate (553 mg, 94%). The pivalate was dissolved in CH$_2$Cl$_2$ (10 ml), and Et$_3$N (0.56 ml, 4.25 mmol) and MeSO$_2$Cl (0.2 ml, 2.55 mmol) were added at 0 °C. The mixture was stirred at 0 °C for 30 min and then treated with MeOH (1 ml). After evaporation of the solvent the residue was purified by flash chromatography with 30% EtOAc in hexane to give the mesylate (610 mg, 100%). The mesylate was dissolved in ether–MeOH (10 ml–5 ml) and excess KH was added at 0 °C. The mixture was stirred for 6 h and extracted with ether. The extract was washed with water and brine, dried, and evaporated. Flash chromatography with 20% EtOAc in hexane gave the epoxide **7** (375 mg, 84% yield). $[\alpha]_D^{25}$ +3.87° (c=0.6, CHCl$_3$). IR (CHCl$_3$): 1422, 1110, 1035, 910 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 1.05 (9H, s, *tert*-Bu), 1.68—1.87 (6H, m), 2.48 (1H, d, J=5.1 Hz), 2.78 (1H, t, J=4.9 Hz), 3.03 (1H, m), 3.33, 3.39 (each 3H, s, 2 × OMe), 3.75 (2H, m), 3.94 (2H, m), 4.62, 4.66 (each 1H, d, J=6.8 Hz, OCH$_2$O), 4.70, 4.73 (each 1H, d, J=6.8 Hz, OCH$_2$O), 7.40 (6H, m), 7.67 (4H, m). HR-EI-MS m/z: Calcd for C$_{28}$H$_{42}$O$_6$Si: 502.2748. Found: 502.2761.

(3*S*,5*R*,7*S*,9*RS*)-7-Acetoxy-3,5-bis(methoxymethoxy)-9-phenyl-9-phenylthio-1-nonanol (8) 1) Coupling Reaction A solution of benzyl phenyl sulfide (445 mg, 2.2 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (0.34 ml, 2.2 mmol) in dry THF (25 ml) was cooled to −40 °C, then 1.6 M *n*-BuLi in hexane (1.4 ml, 2.2 mmol) was added and the solution was stirred for 30 min. To this solution was added a solution of **7** (223 mg, 0.4 mmol) in THF (3 ml) at −40 °C. The mixture was stirred for 2 h at −30 °C then the reaction was quenched with aqueous NH$_4$Cl and the whole was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Flash chromatography with 25% EtOAc in hexane gave a diastereomeric mixture of the adducts (309 mg, 99% yield). IR (CHCl$_3$): 3450,1420, 1105, 1025 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 1.02 (9H, s, *tert*-Bu), 1.50—1.90 (6H), 1.95—2.20 (2H), 3.21 (1H, m), 3.33, 3.39 (each, 3H, s, 2×OMe), 3.55—3.95 (3H, m), 4.49—4.80 (4H, $2\times OCH_2O$), 7.10—7.30 (10H), 7.39 (6H), 7.65 (4H). CI-MS (NH_3) *m/z*: 720 (MNH_4^+).

2) Acetylation and Desilylation The adducts (309 mg) obtained above were treated with pyridine (3 ml) and acetic anhydride (3 ml), and the solution was stirred at room temperature for 15 h. After removal of the solvents *in vacuo* the residue was purified by flash chromatography with 20% EtOAc in hexane to give the acetates (323 mg, 100% yield). The acetates (292 mg, 0.39 mmol) were dissolved in THF (10 ml) and 1.0 M tetra-*n*-butylammonium fluoride (1.2 ml) in THF was added. Stirring was continued for 3 h, then the solvent was evaporated and the residue was purified by flash chromatography with 80% EtOAc in hexane to give **8** as a mixture of two diastereoisomers (189 mg, 95% yield). IR ($CHCl_3$): 3450, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.77, 1.95 (each 0.5H, s, OAc), 3.28, 3.39 (each 3H, s, 2×OMe), 3.58—3.90 (4H), 4.18 (1H, m), 4.54—4.68 (4H, $2\times OCH_2O$), 4.86, 5.12 (each 0.5H, m, CHOAc), 7.22 (10H). CI-MS (NH_3) *m/z*: 524 (MNH_4^+). HR-EI-MS *m/z*: Calcd for $C_{27}H_{38}O_7S$: 506.2336. Found: 506.2359.

Methyl (3*R*,5*R*,7*S*)-7-Acetoxy-3,5-dihydorxy-9-phenyl-9-phenylsulfinylnonanoate (9) and the Corresponding Lactone (10) A solution of **8** (30 mg, 0.06 mmol) in acetone (1 ml) was cooled to 0 °C, then 2.67 M Jones reagent (0.055 ml) was added, and the mixture was stirred at 0 °C for 10 min. Three drops of 2-propanol were added and the whole was extracted with EtOAc. The extract was washed with water, dried, and evaporated to dryness to give an oil. The oil was dissolved in MeOH (5 ml) and Amberlyst-15 (*ca.* 300 mg) was added. After being heated at 40 °C for 7 h the mixture was filtered and the filtrate was concentrated to dryness. Flash chromatography with 2% MeOH in EtOAc gave **9** (12.7 mg, 46%) and **10** (6.0 mg, 24%). Compound **9**: CI-MS (NH_3) *m/z*: 447 (MH^+). Compound **10**: CI-MS (NH_3) *m/z*: 415 (MH^+). Although **9** and **10** showed complicated ^{1}H-NMR spectra because of the presence of a mixture of diastereoisomers, the ^{1}H-NMR spectrum of **9** indicated the presence of a methoxyl signal at 3.70 ppm. Treatment of **9** (36 mg) in CH_2Cl_2 (5 ml) with camphorsulfonic acid (21 mg) for 20 min gave **9** (20.8 mg) and **10** (13.2 mg, 41% yield; 96% yield based on the consumed **9**).

(3*R*,5*R*,7*S*)-7-Acetoxy-3,5-dihydroxy-9-phenyl-8-nonenoic Acid δ-Lactone (11) A solution of the lactone **10** (32 mg) in toluene (5 ml) and pyridine (2 drops) was refluxed for 1 h and after cooling the solvent was evaporated *in vacuo*. Flash chromatography with 10% hexane in EtOAc gave **11** (18 mg, 77% yield) as a single isomer. $[\alpha]_D^{25}$ $-68.1°$ ($c=0.55$, $CHCl_3$). IR ($CHCl_3$): 3580, 3450, 1730, 1365, 1240, 960 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.67 (1H, ddd, $J=13.7$, 11.7, 9.0 Hz), 2.08 (3H, s, OAc), 2.09 (2H, m), 2.28 (1H, m), 2.49 (1H, dd, $J=17.1$, 7.8 Hz), 2.91 (1H, ddd, $J=17.1$, 5.9, 1.2 Hz), 4.30 (1H, m), 4.32 (1H, m), 5.65 (1H, td, $J=7.6$, 4.9 Hz), 6.12 (1H, dd, $J=15.9$, 7.6 Hz), 6.66 (1H, d, $J=15.9$ Hz), 7.30—7.40 (5H). CI-MS (NH_3) *m/z*: 322 (MNH_4^+). HR-EI-MS *m/z*: Calcd for $C_{17}H_{20}O_5$: 304.1273. Found: 304.1291.

Cryptocaryalactone (1) A solution of **11** (13.8 mg) in pyridine (1 ml) and acetic anhydride (1 ml) was stirred for 5 h and then the solvents were removed *in vacuo*. The residue was dissolved in benzene (4ml) and DBU (0.02 ml) was added. After being stirred at room temperature for 1 h the mixture was extracted with EtOAc. The extract was washed with dilute HCl, aqueous $NaHCO_3$, and brine, dried and evaporated to dryness. Flash chromatography with 45% EtOAc in hexane gave 11.6 mg (89% yield) of cryptocaryalactone (**1**), mp 125—126 °C (recrystallized from $CHCl_3$–hexane). $[\alpha]_D^{25}$ $+18.0°$ ($c=0.25$, $CHCl_3$). IR ($CHCl_3$): 3020, 2950, 1730, 1495, 1450, 1425, 1375, 1240, 1160, 1120, 1075, 1035, 965, 820 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.08 (3H, s, OAc), 2.08 (1H, ddd, $J=14.4$, 9.0, 4.4 Hz), 2.20 (1H, ddd, $J=14.4$, 8.3, 4.6 Hz), 2.40 (2H, m), 4.55 (1H, ddd, $J=15.6$, 8.1, 4.4 Hz), 5.65 (1H, m), 6.04 (1H, dt, $J=10.0$, 1.9 Hz), 6.12 (1H, dd, $J=16.1$, 7.3 Hz), 6.67 (1H, d, $J=16.1$ Hz), 6.87 (1H, dt, $J=10.0$, 4.4 Hz), 7.30—7.40 (5H). EI-MS *m/z*: 286 (M^+). HR-EI-MS *m/z*: Calcd for $C_{17}H_{18}O_4$, 286.1204. Found: 286.1190.

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