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Asymmetric Total Synthesis of (+)-Crassalactone D

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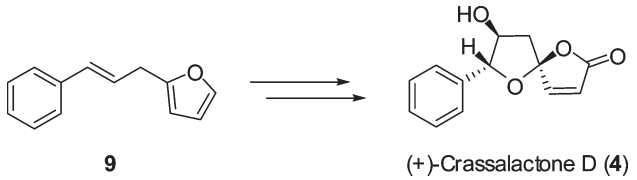

The asymmetric total synthesis of (+)-crassalactone D (**4**), a naturally occurring antitumor agent, has been achieved by employing an oxidative spirocyclization of furan **11** as the key step. Two close analogues, 7-*epi*-crassalactone D (**14**) and 5-*epi*-7-*epi*-crassalactone D (**15**), also have been prepared in the course of the synthesis of (+)-crassalactone D.

Four new styryl-lactones, (+)-crassalactones A−D (**1**−**4**, Figure 1), have been recently isolated from the leaves and twigs of *Polyalthia crassa*.[1] The structure of (+)-crassalactone D (**4**), which possesses a spiroketal chiral center, was elucidated on the basis of spectroscopic methods. The relative configuration of compound **4** was established by single-crystal X-ray diffraction analysis and its absolute stereochemistry was determined as (5*S*,7*S*,8*R*) by NMR studies on (*R*)- and (*S*)-MTPA esters of **4**.[1] Similar to other styryl-lactones, (+)-crassalactone D has shown broad cytotoxic activity against human and rat cancer cell lines.[1] Popsavin and co-workers have accomplished the first total synthesis of crassalactone C (**3**) from D-xylose.[2] More recently, Pavlakos and co-workers reported the first synthesis of crassalactone D and its 4-epimer by a very similar route, but with modest enantiomeric excess.[3] We report herein the asymmetric total synthesis of (+)-crassalactone D (**4**) where high enantioselectivity has been achieved.

In our retrosynthetic analysis, we envisaged that the spiroketal center in lactol **5**, which could serve as the precursor of compound **4**, could be established by spirocyclization of

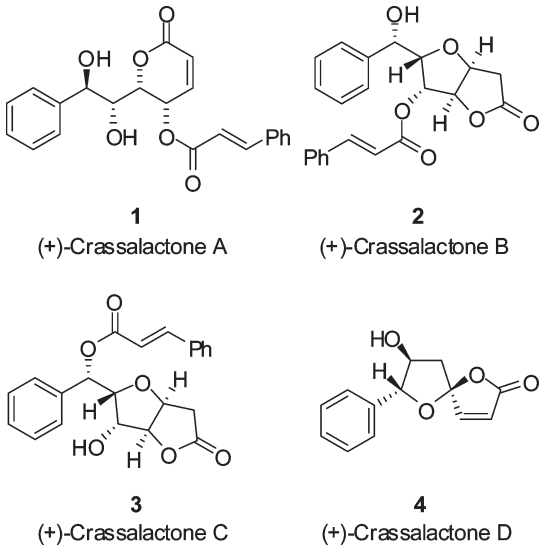

FIGURE 1. The structures of crassalactones A−D (**1**−**4**).

unsaturated keto-aldehyde **6**. The oxidation of furan **7** would provide keto-aldehyde **6**, as described by Robertson in the synthesis of pyrenolide D analogues utilizing *m*-CPBA oxidation of a very similar substrate.[4] The antihydroxyl groups in compound **7** could be generated from either *cis*-olefin **8** or *trans*-olefin **9** (Scheme 1).

Our asymmetric total synthesis of (+)-crassalactone D (**4**) is illustrated in Scheme 2. It has been reported that the asymmetric dihydroxylation of trans olefins[5] provides greater enantioselectivity than cis olefins.[6] Therefore, the known *trans*-olefin **9**[7] was prepared by reaction of the commercially available bromide **10** and 2-furyllithium and subjected to Sharpless asymmetric dihydroxylation to provide the desired diol **11** in 89% yield and greater than 99% ee.[8] Attempts at oxidation of furan **11** with *N*-bromosuccinimide[9] or Rose Bengal-sensitized photooxidation[10] of **11** failed in our hands to provide the desired products. However, oxidative spirocyclization of furan **11** with *m*-CPBA[4,11] worked well and

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(8) The ee value was determined by chiral HPLC on a Chiralcel OJ-H column (250 × 4.6 mm) by comparison to the corresponding (±)-**11**. See the Supporting Information for the preparation of (±)-**11**.

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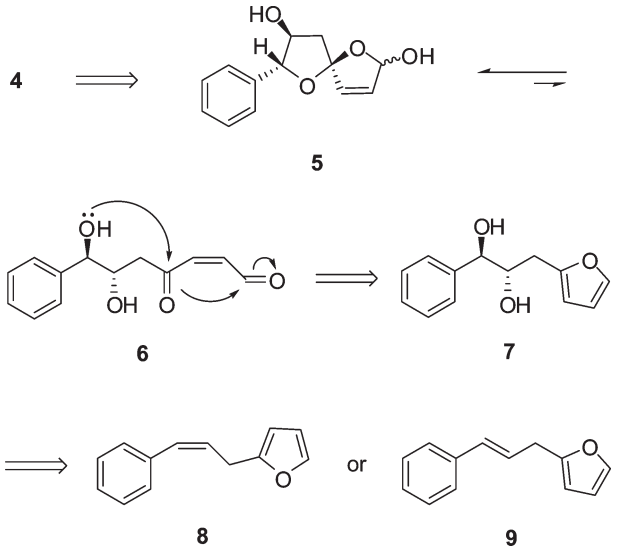
SCHEME 1. Retrosynthetic Analysis of Crassalactone D (4)



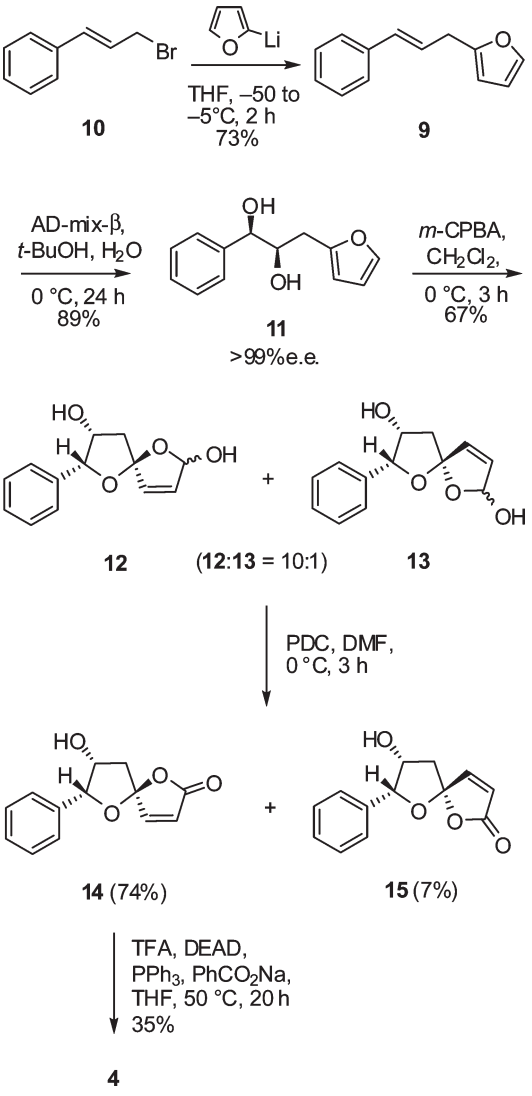
afforded an inseparable mixture of two lactols **12** and **13** in a ratio of 2:1 in the crude reaction mixture by ^{1}H NMR analysis. Interestingly, it was observed that the less stable isomer **13** could be converted to the more stable **12** in a solution of dichloromethane or deuterated chloroform in 24 h to give a 3:1 mixture of **12** and **13** by ^{1}H NMR analysis. Recrystallization of the mixture from dichloromethane by allowing the solvent to evaporate slowly over a period of 3 days significantly improved the ratio to 10:1 by ^{1}H NMR in favor of the desired isomer **12**. The structure of compound **12** was established on the basis of ^{1}H, ^{13}C, 2D-COSY, 2D-HSQC, and 1D-NOE NMR studies. The key NOE correlations of compound **12** are shown in Figure 2.

To further explore the conversion of **12** to **13**, the corresponding acetates **16** and **17** (Figure 2) were prepared from alcohols. The acetates were separable by column chromatography, and their structures were elucidated through interpretation of various one-dimensional (^{1}H, ^{13}C, NOE) and two-dimensional (COSY, HSQC) NMR experiments. Key NOE correlations in **16** and **17** are shown in Figure 2. It was observed that compound **17** was slowly transformed into the more stable **16** in deuterated chloroform to give a mixture of **16** and **17** in a ratio of 3:1 after several days. Therefore, a similar equilibrium between **16** and **17** seems to exist as those observed with **12** and **13**.

Subsequent selective oxidation of the mixture of lactols **12** and **13** with pyridinium dichromate provided 7-*epi*-crassalactone D (**14**) and 5-*epi*-7-*epi*-crassalactone D (**15**), which were separable by chromatography, in 74% and 7% yield, respectively. Results of NMR (^{1}H, ^{13}C, 2D-COSY, and 2D-HSQC) experiments and the diagnostic NOE difference between compounds **14** and **15** (shown in Figure 2) supported the assignment of the structures and stereochemistry of these two lactones and their precursors.

To invert the 7-OH in 7-*epi*-crassalactone D (**14**), a Mitsunobu reaction of **14** with trifluoroacetic acid in the

SCHEME 2. Total Synthesis of Crassalactone D (4)



presence of sodium benzoate[12] was investigated. The reaction was very slow at room temperature on this hindered hydroxyl group, but fortunately occurred at 50 °C to provide (+)-crassalactone D (**4**) in 35% yield, in addition to recovery of lactone **14** in 40% yield. Both ^{1}H and ^{13}C NMR data of compound **4** are consistent with the naturally occurring (+)-crassalactone D[1] and its physical properties are in agreement with those reported in the literature.[13] Finally, the structure of **4** was confirmed by single-crystal X-ray analysis.[14]

In conclusion, starting from inexpensive and readily available starting material and employing Sharpless asymmetric dihydroxylation and furan oxidative spirocyclization, we accomplished a highly enantioselective total synthesis of (+)-crassalctone D, a naturally occurring styryl lactone possessing remarkable in vitro antitumor activity against mammalian cancer cell lines.

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(13) Our optical rotation value $[\alpha]^{20}_D$ is slightly greater than the data for $[\alpha]^{30}_D$ reported in ref 1. A similar result was obtained for synthetic (+)-crassalactone C reported in ref 2a.

(14) See the Supporting Information for more details.

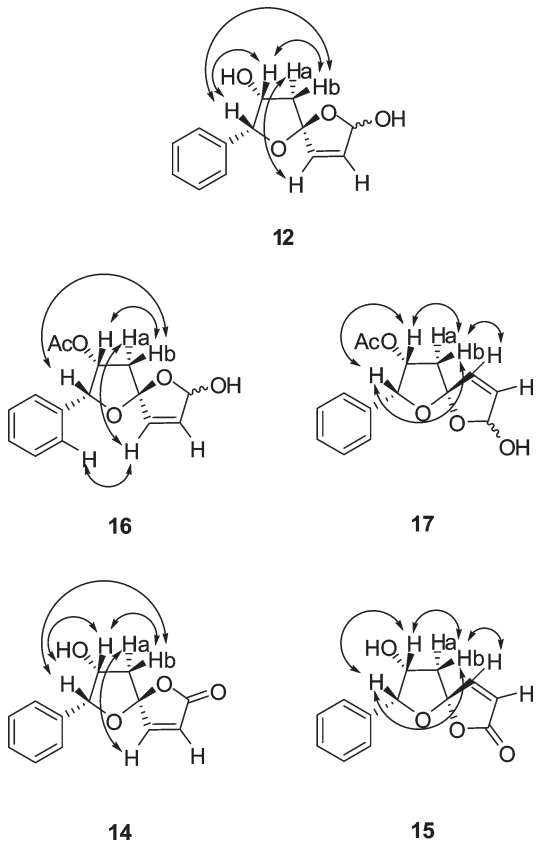

FIGURE 2. Key NOE correlations in **12**, **14**, **15**, **16**, and **17**.

Experimental Section

2-Cinnamylfuran (9). To a solution of furan (1.40 g, 20.6 mmol) in anhydrous THF (20 mL) at −50 °C under nitrogen was added dropwise *tert*-butyllithium (1.7 M in pentane, 9.67 mL, 16.4 mmol). The mixture was allowed to warm to 0 °C and stirred under nitrogen for 3 h. After this time, the mixture was again cooled to −50 °C. Bromide **10** (2.70 g, 13.7 mmol) in THF (10 mL) was added dropwise. The reaction mixture was slowly warmed to −5 °C and then quenched with a saturated solution of ammonium chloride. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0−5% ethyl acetate/hexanes) to give furan **9** (1.83 g, 73%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00−7.38 (m, 6H), 6.49 (d, J = 15.9 Hz, 1H), 6.25−6.35 (m, 2H), 6.07 (dd, J = 3.0, 1.0 Hz, 1H), 3.55 (d, J = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 141.4, 137.3, 132.1, 128.6 (2C), 127.4, 126.3 (2C), 125.6, 110.4, 105.7, 31.8; ESI MS m/z 185 $[M + H]^+$.

(1*R*,2*R*)-3-(Furan-2-yl)-1-phenylpropane-1,2-diol (11). To a mixture of AD-mix-β (1.96 g), methanesulfonamide (0.134 g, 1.40 mmol), *tert*-butanol (7 mL), and water (7 mL) at 0 °C was added 2-cinnamylfuran (**9**, 0.259 g, 1.40 mmol), then the reaction mixture was stirred vigorously at 0 °C for 24 h. After this time, the reaction mixture was quenched with 1 N sodium sulfite (1 mL) and stirred for 1 h at room temperature. The mixture was then extracted with methylene chloride (3 × 10 mL). The combined organic extracts were washed with 2 N potassium hydroxide solution, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography (silica, 0−50% ethyl acetate/hexanes) to afford diol **11** (270 mg, 89%) as a white solid: mp 60−61 °C; $[\alpha]^{20}_D$ +7.5 (c 1.0, CH_3OH); IR (KBr) ν_{max} 3431, 3262, 3146, 3116, 3060, 3026, 2996, 2904, 1603, 1510, 1448, 1323, 1098, 1070, 1003, 932 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.41 (m, 6H), 6.30 (dd, J = 5.0, 2.0 Hz, 1H), 6.11 (dd, J = 3.0, 1.0 Hz, 1H), 4.55 (dd, J = 6.0, 3.0 Hz, 1H), 4.01−4.05 (m, 1H), 2.72−2.81 (m, 3H), 2.43 (d, J = 4.0 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 154.4, 143.4, 142.2, 129.2 (2C), 128.6, 128.1 (2C), 111.2, 107.6, 77.6, 75.4, 33.0; APCI MS m/z 219 $[M + H]^+$; HRMS calcd for $C_{13}H_{15}O_3$ $[M + H]^+$: 219.1021, found: 219.1021; chiral HPLC > 99% ee.

(5*S*,7*R*,8*R*)-7-Phenyl-1,6-dioxaspiro[4.4]non-3-ene-2,8-diol (12). To a solution of furan **11** (250 mg, 1.15 mmol) in dichloromethane (5 mL) at 0 °C under nitrogen was added *m*-CPBA (77%, 336 mg, 1.50 mmol) in portions. The mixture was stirred under nitrogen for 3 h. After this time, the reaction mixture was diluted with ethyl acetate (50 mL), washed with a saturated solution of sodium carbonate (2 × 10 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0−100% ethyl acetate/hexanes) to give a mixture of lactols **12** and **13** as a white solid. The material was dissolved in dichloromethane (10 mL), and the solvent was slowly evaporated over a period of 3 days to provide a mixture of **12** and **13** (180 mg, 67%) in a ratio of 10:1. Analytical data for **12**: IR (KBr) ν_{max} 3410, 3060, 2943, 1498, 1440, 1409, 1277, 1140, 1092, 988, 961, 805 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.43 (m, 5H), 6.26 (d, J = 5.5 Hz, 1H), 6.10 (d, J = 5.5 Hz, 1H), 5.83 (d, J = 9.0 Hz, 1H), 5.33 (d, J = 3.0 Hz, 1H), 4.50 (m, 1H), 2.92 (d, J = 10.0 Hz, 1H), 2.60 (dd, J = 14.5, 5.5 Hz, 1H), 2.39 (dd, J = 14.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5, 134.2, 131.2, 128.7 (2C), 128.3, 126.8 (2C), 116.7, 101.2, 84.9, 74.2, 44.1; ESI MS m/z 257 $[M + Na]^+$; ESI MS m/z 233 $[M - H]^-$; HRMS calcd for $C_{13}H_{14}O_4Na$ $[M + Na]^+$ 257.0790, found 257.0785.

(+)-7-*epi*-Crassalactone D (14) and 5-*epi*-7-*epi*-crassalactone D (15). To a mixture of lactols **12** and **13** (120 mg, 0.51 mmol), 3 Å molecular sieves (100 mg), and DMF (2 mL) at 0 °C under nitrogen was added PDC (290 mg, 0.77 mmol). The mixture was stirred under nitrogen at 0 °C for 4 h. After this time, the reaction mixture was diluted with ethyl acetate (40 mL), washed with water (2 × 20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 0−80% ethyl acetate/hexanes) to give lactone **14** (88 mg, 74%) as a white solid and lactone **15** (8 mg, 7%) as a white solid. Analytical data for **14**: mp 130−132 °C; $[\alpha]^{20}_D$ −64.5 (c 0.3, EtOH); IR (KBr) ν_{max} 3489, 3388, 3140, 2910, 1764, 1612, 1499, 1457, 1408, 1338, 1286, 1178, 1077, 1016, 914 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.44 (m, 6H), 6.15 (d, J = 5.5 Hz, 1H), 5.43 (d, J = 2.5 Hz, 1H), 4.62−4.64 (m, 1H), 2.82 (dd, J = 15.0, 5.0 Hz, 1H), 2.54 (d, J = 15.0 Hz, 1H), 1.34 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 152.9, 134.2, 128.8 (2C), 128.7, 126.7 (2C), 122.8, 113.7, 86.5, 73.8, 43.2; ESI MS m/z 233 $[M + H]^+$; HRMS calcd for $C_{13}H_{13}O_4$ $[M + H]^+$ 233.0814, found 233.0812. Analytical data for **15**: mp 151−154 °C; $[\alpha]^{20}_D$ −48.2 (c 0.2, EtOH); IR (KBr) ν_{max} 3417, 3106, 3080, 2918, 1732, 1605, 1495, 1448, 1420, 1325, 1197, 1107, 1026, 930 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.41 (m, 5H), 7.20 (d, J = 6.0 Hz, 1H), 6.24 (d, J = 6.0 Hz, 1H), 5.39 (d, J = 4.0 Hz, 1H), 4.57−4.60 (m, 1H), 2.64 (dd, J = 14.0, 5.0 Hz, 1H), 2.54 (d, J = 14.0 Hz, 1H), 1.99 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 151.7, 135.2, 128.6 (2C), 128.4, 126.7 (2C), 124.5, 114.1, 88.9, 72.9, 44.3; ESI MS m/z 233 $[M + H]^+$; HRMS calcd for $C_{13}H_{13}O_4$ $[M + H]^+$ 233.0814, found 233.0813.

(+)-Crassalactone D (4). To a solution of lactone **14** (60 mg, 0.26 mmol) in THF (1 mL) at room temperature under nitrogen

was added diethyl azodicarboxylate (54 mg, 0.31 mmol), followed by trifluoroacetic acid (36 mg, 0.31 mmol) and triphenylphosphine (81 mg, 0.31 mmol). The mixture was stirred under nitrogen for 5 min and sodium benzoate (45 mg, 0.31 mmol) was added. The reaction mixture was stirred at room temperature for 2 h and then at 50 °C for 20 h. After this time, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (40 mL), washed with a saturated solution of sodium bicarbonate (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 0−50% ethyl acetate/hexanes) to give lactone **14** (24 mg) and (+)-crassalactone D (**4**, 21 mg, 35%) as a white solid: mp 138−140 °C; $[\alpha]^{20}_{D}$ +13.6 (*c* 0.2, EtOH) {lit.[1] mp 138−139 °C; $[\alpha]^{30}_{D}$ +7.0 (*c* 0.2, EtOH)}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.41 (m, 2H), 7.31−7.34 (m, 3H), 7.29 (d, J = 5.5 Hz, 1H), 6.28 (d, J = 5.5 Hz, 1H), 5.40 (d, J = 2.0 Hz, 1H), 4.42 (dt, J = 6.0, 1.5, 1.5 Hz, 1H), 2.74 (br s, 1H), 2.56 (dd, J = 14.0, 6.5 Hz, 1H), 2.30 (dd, J = 14.0, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 150.9, 138.4, 128.7 (2C), 128.2, 125.0 (2C), 124.9, 114.3, 91.5, 78.2, 42.4; ESI MS m/z 233 $[M + H]^+$; HRMS calcd for $C_{13}H_{13}O_4$ $[M + H]^+$ 233.0814, found 233.0817.

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Supporting Information Available: Crystallographic data of compound **4**, experimental procedures for (±)-**11**, ^{1}H NMR spectra for compound **12**, and ^{1}H and ^{13}C NMR spectra for compounds **11**, **14**, **15**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.