A Chiron Approach for the Total Synthesis of Crassalactone A

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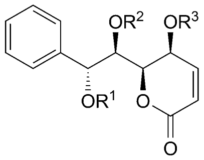
The total synthesis of crassalactone A (**1**) has been achieved in twelve steps starting from commercially available 1,5-D-gluconolactone. *Still–Gennari* olefination, one-pot deprotection, and lactonization are the key reactions involved in the synthesis.

Introduction. – Styryl lactones isolated from *Polyallthia* species have been used as a traditional medicine. The compounds from this species possess antimalarial [1], anti-inflammatory [2], antimicrobial [3], anti-HIV [4], and cytotoxic activities [5]. Among the styryl lactones crassalactone A (**1**), howiinol A (**2**), and tricinnamate (**3**) share the same core skeleton (*Fig.*). Recently, **1** was isolated from a cytotoxic AcOEt extract of the leaves and twigs of *Polyalthia crassa* by *Tuchinda et al.* [6]. Crassalactone A (**1**) exhibited excellent cytotoxic activities against murine lymphocytic leukemia (P-388; ED_{50} 0.18 µg/ml), human nasopharyngeal carcinoma (KB; 1.7 µg/ml), human colon cancer (Col-2; 1.9 µg/ml), human breast cancer (BCA-1; 0.92 µg/ml), human lung cancer (Lu-1; 1.9 µg/ml), and rat glioma (ASK; 1.6 µg/ml). These excellent biological activities have encouraged us to attempt at the total synthesis of crassalactone A (**1**) and its analogs, and to investigate for further pharmacological properties. So far, there is only one total synthesis reported for crassalactone A [7].



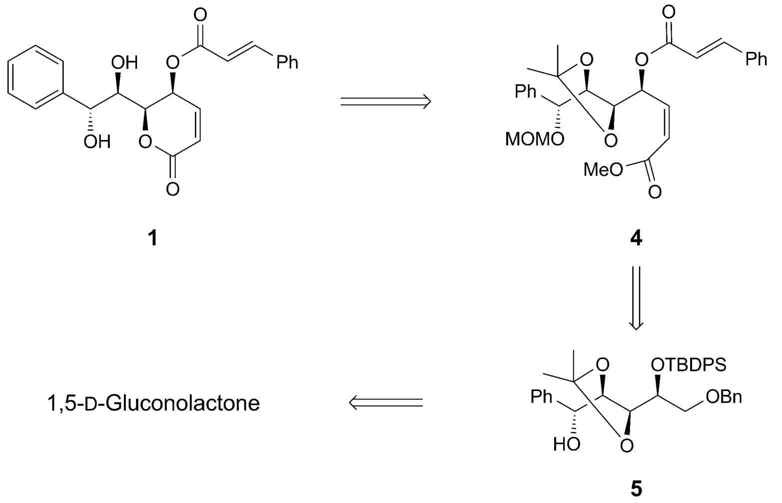
	R^1	R^2	R^3
Crassalactone A (**1**)	H	H	Cinnamoyl
Howiinol A (**2**)	Cinnamoyl	H	H
Tricinnamate (**3**)	Cinnamoyl	Cinnamoyl	Cinnamoyl

Fig. 1. *Structures of some styryl-containing lactones*

As part of our ongoing research program on synthesis of biologically active lactone-containing natural products [8], herein, we report the total synthesis of crassalactone A (**1**) starting from commercially available 1,5-D-gluconolactone in which all four contiguous stereogenic centers are present as required for **1**.

Results and Discussion. – Retrosynthetically, we envisioned crassalactone A (**1**) to be synthesized from intermediate **4** through one-pot acetonide deprotection and lactonization, **4**, in turn, could be obtained from **5** *via* MOM protection, desilylation, cinnamoylation, debenzylation, oxidation, and *Still–Gennari* olefination reaction. The key precursor **5** could be obtained from commercially available 1,5-D-gluconolactone in five steps (*Scheme 1*).

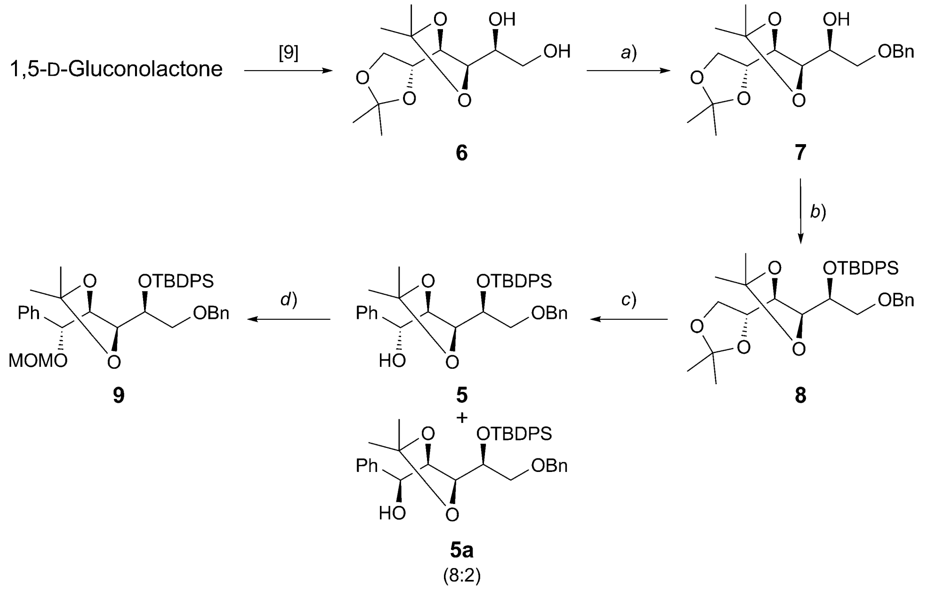
Scheme 1. *Retrosynthetic Analysis of Crassalactone A* (**1**)



The synthesis started from the commercially available, inexpensive 1,5-D-gluconolactone, which was converted to diol **6**, in 65% overall yield, as described in [9]. The primary OH group was selectively protected as the corresponding benzyl ether **7** by using dibutyltinoxide (Bu_2SnO), benzyl bromide (BnBr), and Bu_4NI. The free secondary OH group was masked as the silyl ether **8** by treatment of **7** with ^{t}Bu(Ph)$_2$-SiCl chloride in the presence of NaH (*Scheme 2*).

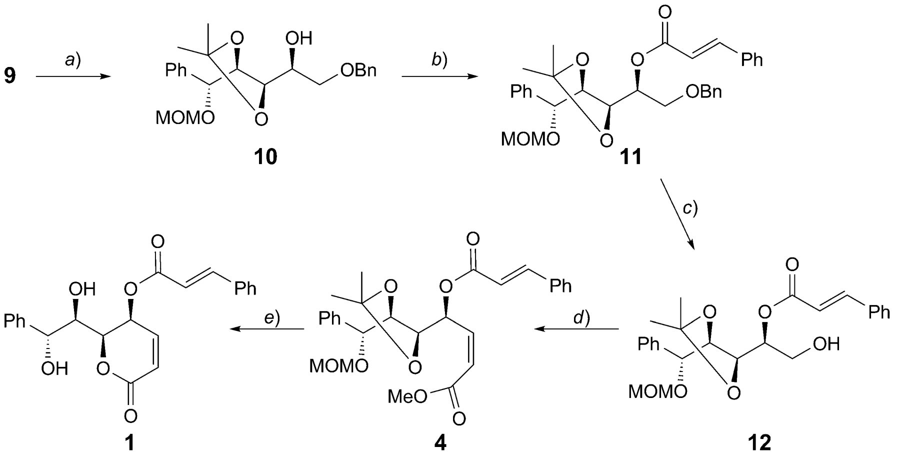
Compound **8** was subjected to 'dehomologation' by one-pot primary acetonide deprotection and degradation of the resulting diol with H_5IO_6 in AcOEt [10] to furnish the aldehyde, which was further subjected to *Grignard* reaction with PhMgBr (*in situ* prepared from PhBr and Mg) to afford an easily separable (column chromatography) diastereoisomer mixture **5**/**5a** (in a ratio of 8:2). The desired major product **5** was treated with methoxymethyl chloride (MOMCl) in the presence of *Hünig*'s base to obtain the corresponding methoxymethyl ether **9** in 85% yield. With all the stereogenic centers fixed, the stage was set to proceed further for cinnamoylation and lactone-ring formation. For this purpose, we proceeded with silyl deprotection of **9** to yield the alcohol **10**, which was coupled to cinnamic acid according to standard protocol to yield ester **11** in 85% yield (*Scheme 3*). Debenzylation with DDQ afforded primary alcohol as the precursor for C_2 homologation reaction and lactonization. Thus, the alcohol **12** was oxidized with 2-iodoxybenzoic acid (IBX) in DMSO to afford the corresponding aldehyde, which was subjected to *cis*-selective *Still–Gennari* olefination reaction with bis(2,2,2-trifluoroethyl) [(methoxycarbonyl)methyl]phosphonate in the presence of NaH to yield the (Z)-α,β-unsaturated ester **4** exclusively in 85% yield [11]. To obtain

Scheme 2



a) Bu_2SnO, BnBr, Bu_4NI (TBAI), reflux, toluene, 12 h; 80%. *b*) NaH, ^{t}Bu$(Ph)_2$SiCl (TBDPSCl), THF, 0° to r.t., 6 h; 90%. *c*) i. H_5IO_6, AcOEt, 0° to r.t., 8 h; 87%; ii. PhBr, Mg, THF, 0° to r.t., 3 h; 76%. *d*) Methoxymethyl (MOM) chloride, EtN^iPr_2, CH_2Cl_2, r.t., 12 h; 85%.

Scheme 3



a) Bu_4NF (TBAF), THF, 0° to r.t., 5 h; 95%. *b*) Cinnamic acid (= (*E*)-3-phenylprop-2-enoic acid), *N,N'*-dicyclohexylcarbodiimide (DCC), 4-(dimethylamino)pyridine, CH_2Cl_2, r.t., 4 h; 91%. *c*) 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2/H_2O, 0° to r.t., 12 h; 72%. *d*) i. 2-Iodoxybenzoic acid (IBX), CH_2Cl_2/DMSO, 0° to r.t, 4 h; ii. $(CF_3CH_2)_2P(O)CH_2COOMe$, NaH, THF, −78°, 1 h; overall yield for two steps 85%. *e*) CF_3COOH (TFA), CH_2Cl_2, H_2O, r.t., 12 h; 65%.

the lactone, we performed an acid-catalyzed one-pot deprotection and cyclization reaction. Thus, compound **4** was treated with CF_3COOH (TFA) in CH_2Cl_2/H_2O to give the desired product crassalactone A (**1**) in 65% yield (*Scheme 3*). The spectroscopic and physical properties of our synthetic compound **1** were in good agreement with the those in the literature [6][7].

Conclusions. – In summary, we have demonstrated an efficient synthetic route for the total synthesis of crassalactone A. The key steps involved in this synthesis are *Still–Gennari* olefination, one-pot deprotection, and lactonization. The total synthesis has been achieved in twelve steps with 8.09% overall yield.

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Experimental Part

General. All reagents were reagent grade and used without further purification, unless specified otherwise. Solvents were distilled prior to use: THF, toluene and Et_2O were distilled from Na and benzophenone ketyl; MeOH from Mg and I_2, and CH_2Cl_2 from CaH_2. All air- or moisture-sensitive reactions were conducted under N_2 or Ar in flame-dried or oven-dried glassware with magnetic stirring. Column chromatography (CC): silica gel (SiO_2; 60–120 mesh or 100–200 mesh) packed in glass columns; technical-grade AcOEt and petroleum ether (PE), distilled prior to use. Optical rotations: digital polarimeter *Jasco DIP-360*, using a 1-ml cell with a 1-dm path length. FT-IR Spectra: on a *PerkinElmer 683 spectrometer* in KBr pellets $CHCl_3$/neat (as mentioned); $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: in $CDCl_3$ or C_6D_6, with 200 or 300-MHz, or 500-MHz spectrometer *Bruker 300* or *Varian Unity* 500, resp., at r.t.; coupling constant J in Hz; the chemical shifts in ppm with TMS as internal standard. ESI-MS and HR-ESI-MS: *Finnigan MAT* instrument.

*(1*S*)-2-(Benzyloxy)-1-[(4*R*,4′*R*,5*R*)-2,2,2′,2′-tetramethyl-4,4′-bi-1,3-dioxol-5-yl]ethanol* (**7**) [12]. A soln. of **6** [9] (10 g, 38.1 mmol) and Bu_2SnO (9.9 g, 40.0 mmol) was mixed azeotropically with toluene/benzene three times on a rotavapor and was then taken in toluene (100 ml) and refluxed for 12 h. After cooling to r.t., BnBr (6.3 ml, 53.0 mmol) and Bu_4NI (21.1 g, 5.7 mmol) were added to the mixture, which was heated at reflux for 1.5 h. The mixture was poured into H_2O (100 ml) and extracted with AcOEt (3 × 40 ml). The combined org. layers were washed with sat. NaCl and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by CC (PE/AcOEt 6 : 4) to give **7** (10.75 g, 80%). Colorless oil. $[\alpha]_D^{25} = +4.60$ ($c = 1.55$, $CHCl_3$). IR (neat): 3479, 2988, 2928, 1627, 1375, 1247, 1214, 1151, 1070, 846. ^1H-NMR (300 MHz, $CDCl_3$): 7.34–7.20 (*m*, 5 H); 4.58 (*dd*, $J = 12.0, 8.3$, 2 H); 4.17–4.10 (*m*, 1 H); 4.02–3.92 (*m*, 5 H); 3.59 (*d*, $J = 7.5$, 2 H); 2.42 (*d*, $J = 7.7$, 1 H); 1.40 (*s*, 3 H); 1.38 (*s*, 3 H); 1.37 (*s*, 3 H); 1.33 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 137.9; 128.2; 127.6; 127.5; 109.5; 109.3; 80.0; 77.0; 76.9; 73.1; 71.9; 68.8; 67.6; 27.0; 26.7; 26.4; 25.1. ESI-MS: 375 ($[M + Na]^+$). HR-ESI-MS: 375.1797 ($[M + Na]^+$, $C_{19}H_{28}NaO_6^+$; calc. 375.1784).

*{(1*S*)-2-(Benzyloxy)-1-[(4*R*,4′*R*,5*S*)-2,2,2′,2′-tetramethyl-4,4′-bi-1,3-dioxol-5-yl]ethoxy}(*tert*-butyl)-(diphenyl)silane* (**8**). Alcohol **7** (1.0 g, 2.84 mmol) in THF (7 ml) was added to NaH (0.227 g, 5.68 mmol) in THF (3ml) at 0°. The mixture was warmed to r.t. for 1 h and TBDPSCl (0.72 ml, 2.84 mmol) was added at 0°. After warming to r.t. for 7 h, sat. NH_4Cl (3 ml) was slowly added to the mixture at 0°. The mixture was poured into H_2O (5 ml) and extracted with AcOEt (3 × 10 ml). The combined org. layers were washed with H_2O (3 × 5 ml) and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by CC (PE/AcOEt 8 : 2) to give **8** (1.47 g, 90%). Colorless oil. $[\alpha]_D^{25} = +33.70$ ($c = 1.9$, $CHCl_3$). IR (neat): 2927, 2857, 1460, 1374, 1216, 1073, 770. ^1H-NMR (300 MHz, $CDCl_3$): 7.75–7.65 (*m*, 4 H); 7.46–7.27 (*m*, 6 H); 7.24–7.17 (*m*, 3 H); 6.98–6.91 (*m*, 2 H); 4.24 (*t*, $J = 7.1$, 1 H); 4.14–3.96 (*m*, 6 H); 3.83 (*t*, $J = 7.1$, 1 H); 3.55 (*dd*, $J = 9.4, 5.4$, 1 H); 3.41 (*dd*, $J = 9.2, 5.4$, 1 H); 1.48 (*s*, 3 H); 1.38 (*s*, 3 H); 1.31 (*s*, 6 H); 1.03 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 137.7; 135.7; 135.5; 134.5; 134.5;

133.0; 129.4; 129.2; 127.7; 127.4; 127.1; 109.3; 109.2; 80.7; 76.8; 76.5; 72.5; 71.4; 71.3; 67.4; 27.2; 26.9; 26.7; 26.2; 25.1; 19.3. ESI-MS: 613 ($[M+Na]^+$). HR-ESI-MS: 613.2934 ($[M+Na]^+$, $C_{35}H_{46}NaO_6Si^+$; calc. 613.2961).

*(*R*)-{(4*R*,5*S*)-5-[(1*S*)-2-(Benzyloxy)-1-{[(*tert*-butyl)(diphenyl)silyl]oxy}ethyl]-2,2-dimethyl-1,3-dioxolan-4-yl}(phenyl)methanol* (**5**). To a soln. of **8** (1 g, 1.73 mmol) in AcOEt (10 ml) cooled to 0°. H_5IO_6 (0.79 g, 3.47 mmol) was added, and the soln. was allowed to warm to r.t. for 12 h. The reaction was quenched by the addition H_2O (5 ml), the mixture was extracted with AcOEt (10 ml), and the combined org. layers were washed with brine (3 ml) and dried (Na_2SO_4). The solvent was removed under reduced pressure, resulting in the formation of an aldehyde (0.761 g, 87%), which was immediately used for the next step without further purification.

To a soln. of *Grignard* reagent (prepared *in situ* from Mg (0.07 g, 2.92 mmol) and PhBr (0.23 ml, 2.2 mmol) in THF (5 ml)) at $-5°$ was added a soln. of the crude aldehyde (0.76 g, 1.46 mmol) in THF. Progress of the reaction was monitored by TLC, and after completion the reaction was cautiously quenched by addition of sat. NH_4Cl (5 ml). The mixture was then poured into H_2O (10 ml) and extracted with Et_2O (3 × 7 ml). Combined Et_2O extracts were washed with brine (4 ml) and dried (Na_2SO_4). After evaporation of the solvent on rotavapor, the residue was purified by CC (SiO_2; PE/AcOEt 9 : 1) to yield **5** (0.529 g, 60.8%) as a pale-yellow liquid, and a minor isomer **5a** (0.132 g, 15.2%). $[\alpha]_D^{25} = +24.2$ ($c = 1.6$, $CHCl_3$). IR (neat): 3451, 2930, 2858, 1374, 1107, 701. ^1H-NMR (300 MHz, $CDCl_3$): 7.60–7.56 (*m*, 2 H); 7.55–7.45 (*m*, 2 H); 7.40–7.21 (*m*, 11 H); 7.20–7.15 (*m*, 3 H); 6.91–6.86 (*m*, 2 H); 4.58 (*d*, $J = 6.0$, 1 H); 4.39 (*dd*, $J = 8.3, 6.0$, 1 H); 4.10 (*dd*, $J = 7.5, 2.2$, 1 H); 3.87 (*q*, $J = 11.3, 9.0$, 2 H); 3.42–3.32 (*m*, 2 H); 1.45 (*s*, 6 H); 1.00 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 140.1; 138.0; 135.8; 135.6; 133.0; 129.6; 129.4; 128.5; 128.0; 127.5; 127.3; 127.2; 126.9; 109.7; 80.3; 78.5; 75.0; 72.5; 70.8; 70.7; 27.6; 27.3; 26.9; 19.5. ESI-MS: 619 ($[M+Na]^+$). HR-ESI-MS: 619.2934 ($[M+Na]^+$, $C_{37}H_{44}NaO_5Si^+$; calc. 619.2956).

*[(1*S*)-2-(Benzyloxy)-1-{(4*S*,5*R*)-5-[(*R*)-(methoxymethoxy)(phenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}ethoxy](*tert*-butyl)(diphenyl)silane* (**9**). EtN^iPr_2 (2.60 ml, 15.1 mmol) and MOM-Cl (0.56 ml, 7.5 mmol) were added to a stirred soln. of **5** (1.5 g, 2.51 mmol) in dry CH_2Cl_2 (15 ml) at 0°. After stirring for 15 min at 0°, the mixture was warmed to r.t. for 12 h. The reaction was quenched with H_2O, and the mixture was extracted with CH_2Cl_2 (3 × 10 ml). Combined org. layers were washed with brine (5 ml) and dried (Na_2SO_4). Evaporation of the solvent, the residue was purified by CC (SiO_2; PE/AcOEt 9.5 : 0.5) to yield **9** (1.36 g, 85%). Pale-yellow liquid. $[\alpha]_D^{25} = +58.0$ ($c = 0.3$, $CHCl_3$). IR (neat): 2932, 2858, 1455, 1213, 1107, 702. ^1H-NMR (300 MHz, $CDCl_3$): 7.67–7.61 (*m*, 2 H); 7.56–7.51 (*m*, 2 H); 7.44–7.23 (*m*, 12 H); 7.18–7.12 (*m*, 3 H); 6.88–6.82 (*m*, 1 H); 4.69–4.50 (*m*, 5 H); 4.03 (*d*, $J = 7.5$, 1 H); 3.75 (*q*, $J = 12.0, 11.3$, 2 H); 3.37 (*s*, 3 H); 3.15–3.00 (*m*, 2 H); 1.46 (*s*, 3 H); 1.30 (*s*, 3 H); 1.05 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.1; 137.2; 135.7; 135.5; 134.5; 133.2; 129.5; 129.3; 128.4; 128.2; 127.9; 127.4; 127.3; 127.0; 109.7; 93.5; 79.4; 78.7; 78.4; 71.9; 70.6; 70.0; 55.3; 27.5; 27.4; 26.8; 19.5. ESI-MS: 663 ($[M+Na]^+$). HR-ESI-MS: 663.3101 ($[M+Na]^+$, $C_{39}H_{48}NaO_6Si^+$; calc. 663.3118).

*(1*S*)-2-(Benzyloxy)-1-{(4*R*,5*R*)-5-[(*R*)-(methoxymethoxy)(phenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}ethanol* (**10**). Bu_4NF (37.5 ml, 37.5 mmol) was added to stirred soln. of **9** (12 g, 18.7 mmol) in THF (120 ml) at 0°. The mixture was stirred for 5 h for r.t., and the reaction was quenched with H_2O (15 ml). The resulting mixture was diluted with AcOEt (3 × 50 ml). The org. phase was successively washed with H_2O (20 ml) and brine (20 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by CC (PE/AcOEt 8 : 2) to afforded **10** (7.13 g, 95%). Colorless oil. $[\alpha]_D^{25} = -25.0$ ($c = 0.3$, $CHCl_3$). IR (neat): 3451, 2930, 1452, 1374, 1101, 1031, 701. ^1H-NMR (300 MHz, $CDCl_3$): 7.33–7.18 (*m*, 10 H); 4.64 (*d*, $J = 6.8$, 1 H); 4.55 (*dd*, $J = 18.1, 6.6$, 1 H); 4.51 (*d*, $J = 6.8$, 1 H); 4.39–4.36 (*m*, 2 H); 4.31 (*t*, $J = 7.7$, 1 H); 3.85 (*t*, $J = 7.9$, 1 H); 3.33 (*s*, 3 H); 3.32–3.21 (*m*, 3 H); 2.89 (br. *s*, 1 H); 1.42 (*s*, 3 H); 1.35 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 137.9; 136.8; 128.4; 128.4; 128.2; 128.0; 127.5; 127.4; 109.7; 93.7; 79.2; 78.7; 77.3; 72.8; 71.5; 68.0; 55.3; 27.1. ESI-MS: 425 ($[M+Na]^+$). HR-ESI-MS: 425.1941 ($[M+Na]^+$, $C_{23}H_{30}NaO_6^+$; calc. 425.1940).

*(1*S*)-2-(Benzyloxy)-1-{(4*R*,5*R*)-5-[(*R*)-(methoxymethoxy)(phenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}ethyl (2*E*)-3-Phenylprop-2-enoate* (**11**). Cinnamic acid (4.04 g, 27.3 mmol), DCC (4.20 g, 20.4 mmol), and DMAP (30 mg) were added to a soln. of **11** (5.5 g, 13.6 mmol) in CH_2Cl_2 (70 ml) at r.t., and stirred for 4 h. After completion of the reaction, the mixture was filtered through a short pad of *Celite*. The filtrate was washed with AcOEt (3 × 15 ml), and combined org. extracts were washed with

brine (20 ml) and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by CC (PE/AcOEt 9:1) to yield **11** (6.58 g, 91%). White solid. $[\alpha]_D^{25} = +4.60$ ($c = 1.55$, $CHCl_3$). M.p. 139–140° IR (neat): 3440, 3252, 2929, 1711, 1642, 1163, 701. ^1H-NMR (300 MHz, $CDCl_3$): 7.67 (*d*, $J = 15.8$, 1 H); 7.53–7.46 (*m*, 2 H); 7.41–7.18 (*m*, 13 H); 6.39 (*d*, $J = 15.8$, 1 H); 4.69–4.65 (*m*, 1 H); 4.59–4.49 (*m*, 3 H); 4.38 (*s*, 2 H); 4.12 (*d*, $J = 3.7$, 2 H); 3.54–3.43 (*m*, 2 H); 3.32 (*s*, 3 H); 1.44 (*s*, 3 H); 1.37 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 165.9; 145.4; 137.9; 136.7; 134.2; 130.3; 128.8; 128.6; 128.5; 128.2; 128.1; 128.0; 127.5; 127.4; 117.5; 110.1; 93.8; 79.3; 78.5; 76.3; 72.6; 69.5; 68.4; 55.4; 27.3; 27.1. ESI-MS: 555 ($[M + Na]^+$). HR-ESI-MS: 555.2360 ($[M + Na]^+$, $C_{32}H_{36}NaO_7^+$; calc. 555.2359).

(1S)-2-Hydroxy-1-{(4R,5R)-5-[(R)-(methoxymethoxy)(phenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}ethyl (2E)-3-Phenylprop-2-enoate (**12**). DDQ (7.4 g, 33.0 mmol) was added to a stirred soln. of **11** (8.8 g, 16.5 mmol) in CH_2Cl_2 (90 ml) and H_2O (10 ml) at 0°. The mixture was stirred for 12 h at r.t., and the reaction was quenched by the addition of 10 ml of sat. $NaHCO_3$. The layers were separated, and the aq. layer was extracted twice with CH_2Cl_2 (3 × 30 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by CC (SiO_2; PE/AcOEt 8:2) to give **12** (5.25 g, 72%). Yellow oil. $[\alpha]_D^{25} = +8.7$ ($c = 0.4$, $CHCl_3$). IR (neat): 3462, 2933, 1712, 1635, 1165, 1031, 765. ^1H-NMR (300 MHz, $CDCl_3$): 7.70 (*d*, $J = 15.8$, 1 H); 7.55–7.50 (*m*, 2 H); 7.41–7.29 (*m*, 8 H); 6.43 (*d*, $J = 15.8$, 1 H); 4.71 (*d*, $J = 6.0$, 1 H); 4.57 (*q*, $J = 15.8$, 6.8, 2 H); 4.23 (*t*, $J = 6.0$, 2 H); 4.07 (*dd*, $J = 7.5$, 2.2, 1 H); 3.70–3.65 (*m*, 2 H); 3.35 (*s*, 3 H); 1.49 (*s*, 3 H); 1.38 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 166.5; 145.8; 136.5; 134.1; 130.5; 128.9; 128.7; 128.2; 128.0; 127.8; 117.3; 110.4; 93.9; 79.2; 78.5; 77.7; 72.1; 63.0; 55.5; 27.2; 27.0. ESI-MS: 465 ($[M + Na]^+$). HR-ESI-MS: 465.1907 ($[M + Na]^+$, $C_{25}H_{30}NaO_7^+$; calc. 465.1889).

Methyl (2E)-4-{(4R,5R)-5-[(R)-(Methoxymethoxy)(phenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-4-{[(2E)-3-phenylprop-2-enoyl]oxy}but-2-enoate (**4**). IBX (0.70 g, 2.26 mmol) and DMSO (2 ml) were added to a stirred soln. of **12** (0.5 g, 1.13 mmol) in anh. CH_2Cl_2 (7 ml) under N_2 at r.t., and stirred for 4 h. After completion of the reaction, the mixture was diluted with Et_2O (15 ml) and filtered through a pad of *Celite*, and the filtrate was washed with sat. $NaHCO_3$ (20 ml). The combined org. layers were dried (Na_2SO_4) and concentrated under vacuum. The crude aldehyde formed was immediately used for the further reaction without purification.

In a 50-ml round-bottom flask, NaH (0.068 g, 1.70 mmol) was taken in 4 ml of dry THF under N_2. After 5 min, bis(2,2,2-trifluoroethyl) [(methoxycarbonyl)methyl)]phosphonate (0.54 ml, 1.70 mmol) was added at 0°, and the mixture was stirred for 30 min. The mixture was cooled to −78°, and the aldehyde (0.50 g, 1.13 mmol) in dry THF (5 ml) was added during 10 min, and the resulting mixture was stirred for 1 h at −78°. The reaction was quenched with sat. NH_4Cl (5 ml), and the mixture was extracted with AcOEt (10 ml). The combined org. layers were concentrated under reduced pressure to give a residue, which was purified by CC (SiO_2; PE/AcOEt 9:1) to furnish **4** (0.476 g, 85%). Yellow liquid. $[\alpha]_D^{25} = -15.0$ ($c = 1.0$, $CHCl_3$). IR (neat): 2931, 1720, 1636, 1202, 1159, 1029, 767. ^1H-NMR (300 MHz, $CDCl_3$): 7.66 (*d*, $J = 15.8$, 1 H); 7.54–7.47 (*m*, 2 H); 7.40–7.26 (*m*, 8 H); 6.38 (*d*, $J = 15.8$, 1 H); 6.08 (*dd*, $J = 8.3$, 3.7, 1 H); 5.92–5.78 (*m*, 2 H); 4.72 (*d*, $J = 6.0$, 1 H); 4.60 (*d*, $J = 6.8$, 1 H); 4.54 (*d*, $J = 6.8$, 1 H); 4.28–4.19 (*m*, 2 H); 3.74 (*s*, 3 H); 3.33 (*s*, 3 H); 1.49 (*s*, 3 H); 1.33 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 165.7; 165.4; 143.2; 137.0; 134.1; 130.4; 128.8; 128.3; 128.1; 121.5; 117.4; 110.3; 94.0; 79.4; 78.8; 77.9; 70.0; 55.6; 51.5; 27.3; 27.1. ESI-MS: 519 ($[M + Na]^+$). HR-ESI-MS: 519.1988 ($[M + Na]^+$, $C_{28}H_{32}NaO_8^+$; calc. 519.1995).

Crassalactone A (=(2S,3S)-2-[(1R,2R)-1,2-Dihydroxy-2-phenylethyl]-6-oxo-3,6-dihydro-2H-pyran-3-yl (2E)-3-Phenylprop-2-enoate; **1**). TFA (0.1 ml) was added to a stirred soln. of **4** (0.03 g, 0.060 mmol) in CH_2Cl_2 (3 ml)/H_2O (0.02 ml) at 0°, and the mixture was allowed to warm to r.t. for 12 h. The reaction was quenched with sat. $NaHCO_3$ (1 ml), and the mixture was extracted with CH_2Cl_2 (3 × 2 ml), and the extract was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to provide a residue, which was purified by CC (SiO_2; PE/AcOEt 6:4) to furnish **1** (0.015 g, 65%). White solid. $[\alpha]_D^{25} = +317.0$ ($c = 0.4$, $CHCl_3$). M.p. 132–134°. IR (neat): 3424, 2924, 2854, 1750, 1711, 1168, 763. ^1H-NMR (300 MHz, $CDCl_3$): 7.62 (*d*, $J = 16.0$, 1 H); 7.51–7.30 (*m*, 10 H); 7.01 (*dd*, $J = 9.5$, 5.6, 1 H); 6.35 (*d*, $J = 16.0$, 1 H); 6.20 (*d*, $J = 9.6$, 1 H); 5.29 (*dd*, $J = 5.6$, 2.6, 1 H); 4.90 (*d*, $J = 5.8$, 1 H); 4.77 (*dd*, $J = 5.8$, 2.6, 1 H); 4.27 (*m*, 1 H), 2.05 (br. *s*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 165.6; 162.4; 146.6; 140.6; 139.8;

133.8; 130.8; 128.9; 128.7; 128.4; 128.2; 126.5; 123.5; 116.4; 77.5; 73.6; 73.4; 62.6. ESI-MS: 403 ($[M+Na]^+$). HR-ESI-MS: 403.1151 ($[M+Na]^+$, $C_{22}H_{20}NaO_6^+$; calc. 403.1158).

REFERENCES

[1] S. Kanokmedhakul, K. Kanokmedhakul, D. Yodbuddee, N. Phonkerd, *J. Nat. Prod.* **2003**, *66*, 616.

[2] M. A. Mosaddik, M. E. Haque, M. A. Rashid, *Biochem. Syst. Ecol.* **2000**, *28*, 1039.

[3] S. Faizi, R. A. Khan, S. Azher, S. A. Khan, S. Tauseef, A. Ahmad, *Planta Med.* **2003**, *69*, 350; M. M. Murthy, M. Subramanyam, M. H. Bindu, J. Annapurna, *Fitoterapia* **2005**, *76*, 336.

[4] H.-Y. Li, N.-J. Sun, Y. Kashiwada, L. Sun, J. V. Snider, L. M. Cosentino, K.-H. Lee, *J. Nat. Prod.* **1993**, *56*, 1130; P. Tuchinda, M. Phomakotr, V. Reutrakul, W. Thanyachareon, S. Sophasan, C. Yoosook, T. Santisuk, J. M. Pezzuto, *Planta Med.* **2001**, *67*, 572.

[5] Y.-C. Wu, C.-Y. Duh, S.-K.Wang, K.-S. Chen, T.-H. Yang, *J. Nat. Prod.* **1990**, *53*, 1327; G. Zhao, J. H. Jung, D. L. Smith, K. V. Wood, J. L. McLaughlin, *Planta Med.* **1991**, *57*, 380; X. Ma, I.-S. Lee, H.-B. Chai, K. Zaw, N. R. Fransworth, D. D. Soejarto, G. A. Cordell, J. M. Pezzuto, A. D. Kinghorn, *Phytochemistry* **1994**, *37*, 1659; C.-Y. Chen, F.-R. Chang, Y.-C. Shih, T.-J. Hsieh, Y.-C. Chia, H.-Y. Tseng, H.-C. Chen, S.-J. Chen, M.-C. Hsu, Y.-C. Wu, *J. Nat. Prod.* **2000**, *63*, 1475.

[6] P. Tuchinda, B. Munyoo, M. Pohmakotr, P. Thinapong, S. Sophasan, T. Santisuk, V. Reutrakul, *J. Nat. Prod.* **2006**, *69*, 1728.

[7] V. Sekhar, D. K. Reddy, V. Suresh, D. C. Babu, Y. Venkateswarlu, *Tetrahedron Lett.* **2010**, *51*, 946.

[8] J. S.Yadav, B. Ganganna, D. C. Bhunia, *Synthesis* **2012**, *44*, 1365; G. Sabitha, A. Y. Reddy, J. S. Yadav *Tetrahedron Lett.* **2012**, *53*, 5624; B. P. Reddy, T. Pandurangam, J. S. Yadav, B. V. S. Reddy, *Tetrahedron Lett.* **2012**, *53*, 5749; J. S. Yadav, B. Thirupathaiah, V. K. Singh, V. Ravishashidhar, *Tetrahedron: Asymmetry* **2012**, *23*, 931; J. S. Yadav, S. S. Mandal, *Tetrahedron Lett.* **2011**, *52*, 5747; J. S. Yadav, S. S. Mandal, J. S. S. Reddy, P. Srihari, *Tetrahedron* **2011**, *67*, 4620; J. S. Yadav, J. S. S. Reddy, S. S. Mandal, P. Srihari, *Synlett* **2010**, 2636; P. Srihari, B. Kumaraswamy, G. M. Rao, J. S. Yadav, *Tetrahedron: Asymmetry* **2010**, *21*, 106; P. Srihari, G. M. Rao, R. S. Rao, J. S.Yadav, *Synthesis* **2010**, 2407; P. Srihari, E. V. Bhasker, A. B. Reddy, J. S. Yadav, *Tetrahedron Lett.* **2009**, *50*, 2420.

[9] J. S. Yadav, B. Madhavarao, K. S. Rao, *Synlett* **2009**, 3179; J. S. Yadav, B. M. Rao, K. S. Rao, *Tetrahedron: Asymmetry* **2009**, *20*, 1725; J. S. Yadav, B. M. Rao, K. S. Rao, B. V. S. Reddy, *Synlett* **2008**, 1039; J. Zhu, D. Ma, *Angew. Chem., Int. Ed.* **2003**, *42*, 5348.

[10] W. Wu, Y. Wu, *J. Org. Chem.* **1993**, *58*, 3586.

[11] W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, *24*, 4405.

[12] Y. Jagadeesh, J. S. Reddy, B. V. Rao, J. L. Swarnalatha, *Tetrahedron* **2010**, *66*, 1202; K.-G. Liu, S. Yan, Y.-L. Wu, Z.-J. Yao, *J. Org. Chem.* **2002**, *67*, 6758.

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