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Synthesis of naturally occurring bioactive butyrolactones: maculalactones A–C and nostoclide I☆

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Abstract—Starting from citraconic anhydride (**13**), a simple multistep (9–10 steps) synthesis of naturally occurring butyrolactones maculalactone A (**3**), maculalactone B (**1**), maculalactone C (**2**) and nostoclide I (**4**) have been described with good overall yields via dibenzylmaleic anhydride (**20**) and benzylisopropylmaleic anhydride (**27**). The two anhydrides **20** and **27** were prepared by S_N2' coupling reactions of appropriate Grignard reagents with dimethyl bromomethylfumarate (**14**), LiOH-induced hydrolysis of esters to acids, bromination of carbon–carbon double bond, in situ dehydration followed by dehydrobromination and chemoselective allylic substitution of bromoatom in disubstituted anhydrides **19** and **26** with appropriate Grignard reagents. The $NaBH_4$ reduction of these anhydrides **20** and **27** furnished the desired lactones **21** and **29**, respectively. The lactone **21** on Knoevenagel condensation with benzaldehyde, furnished maculalactone B (**1**), which on isomerization gave maculalactone C (**2**). Selective catalytic hydrogenation of **1** gave maculalactone A (**3**). The conversion of lactone **29** to nostoclide I (**4**) is known.

1. Introduction

A very large number of natural and unnatural butyrolactones are known in the literature.[1] Recently several diverse skeletons with butyrolactone as a core unit have been isolated as bioactive natural products[2–11] and some of them have been depicted in Figure 1. These butyrolactones possess cytotoxic, antibiotic and antimicrobial activities.[3,6,8] Maculalactones A–C have been isolated from the epilithic-encrusting cyanobacterium *Kyrtuthrix maculans* from Hong Kong island and they possess marine anti-fouling activity.[2,12] The natural (+)-maculalactone A has been assigned *S*-configuration. To date only one synthesis of these butyrolactones **1**-**3** has been reported in the literature.[12] Nostoclide I (**4**) has been isolated from the culture of a symbiotic blue-green alga, *Nostoc* sp., from the lichen *Peltigera canina* and it has cytotoxic activity.[3] To date two syntheses of **4** are known in the literature.[13] These butyrolactones are generally synthesized via Stobbe condensation,[12] Stille coupling reaction[13b] and conversion of furan to the required lactone.[13a] Since 1997, using cyclic anhydrides as potential precursors, we have designed several bioactive natural products in our group.[14] We felt that the synthesis of suitably disubstituted maleic anhydrides, followed by their reductive conversion to the respective lactones, and then the Knoevenagel condensation with different aldehydes will provide an easy access to these novel butenolide skeletons. In continuation of our ongoing studies on cyclic anhydrides to bioactive natural products,[14] now we herein report the synthesis of naturally occurring maculalactones A–C (**3**,**1**,**2**) and nostoclide I (**4**), starting from citraconic anhydride (**13**) via the unsymmetrical bromomethylmaleic anhydrides **19** and **26** (Schemes 1 and 2).

2. Results and discussion

Recently, we studied the NBS-allylic bromination of dimethyl methylmaleate,[15] chemoselective S_N2' coupling reactions of Grignard reagents prepared from primary alkyl halides with dimethyl bromomethylfumarate (**14**) in absence of CuI,[16–18] and chemoselective allylic substitution of bromide in (bromomethyl)methylmaleic anhydride with Grignard reagents prepared from primary alkyl halides in presence of CuI,[19] to design the bioactive natural products. Using these reactions we designed natural products 1,7 (*Z*)-nonadecadiene-2,3-dicarboxylic acid,[16] chaetomellic acid A,[16] 2-(β-carboxyethyl)-3-hexylmaleic, 2-(β-carboxyethyl)-3-octylmaleic and 2-carboxymethyl-3-hexylmaleic anhydrides[17,18] and unnatural products isochaetomellic acid B, 2,3-dihexylmaleic anhydride and 2,3-dioctylmaleic

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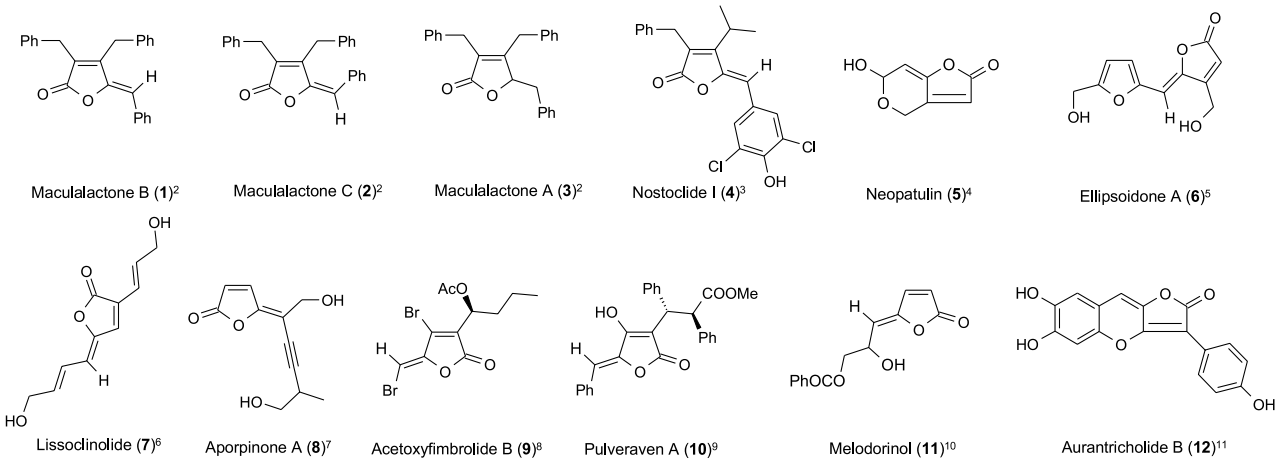
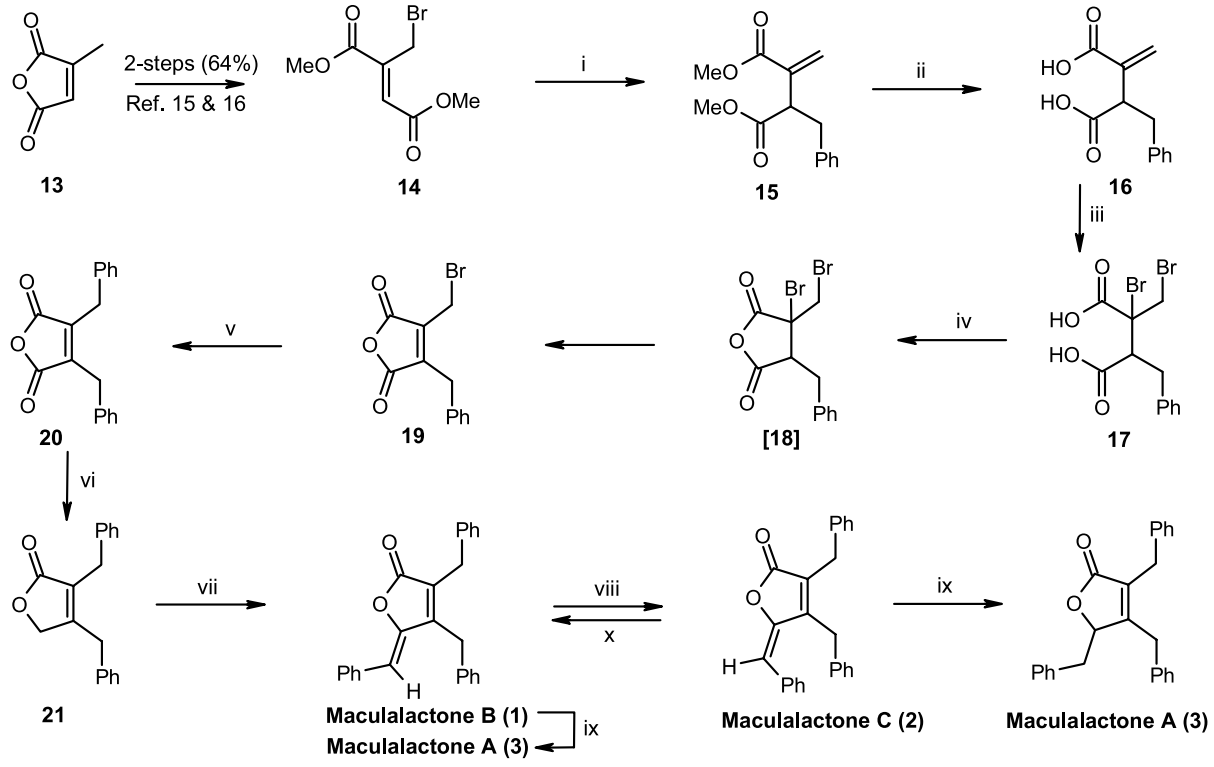
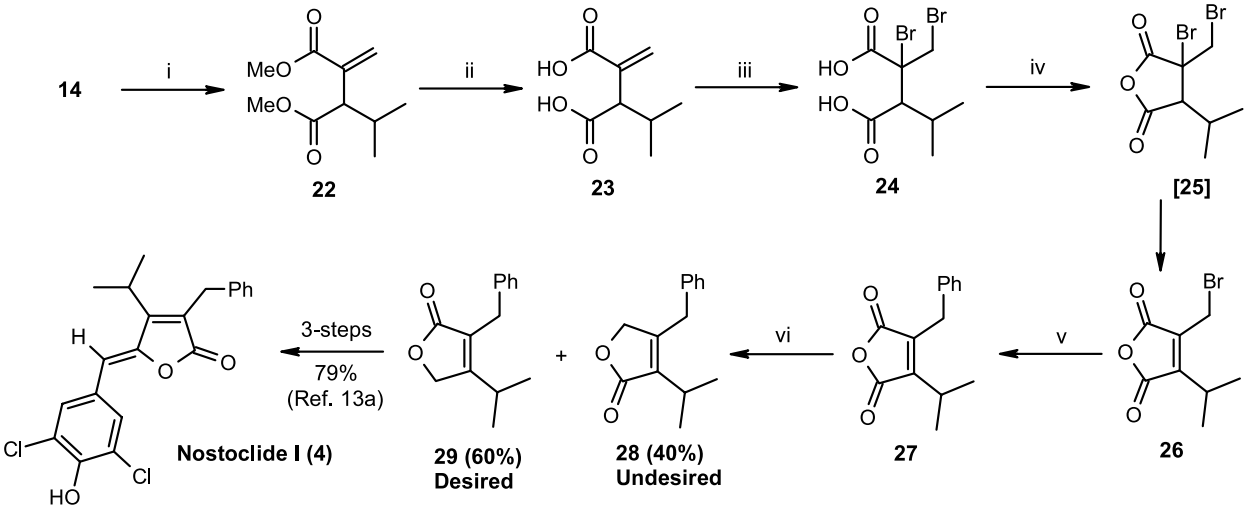


Figure 1. Naturally occurring bioactive butyrolactones and analogs.

anhydride.[16–18] Herein, we planned to study the above two coupling reactions with Grignard reagents from secondary alkyl halides, benzyl halides and aryl halides to design the desired substituted maleic anhydrides **20** and **27**. Citraconic anhydride (**13**) was converted to bromodiester **14** in 2-steps with 64% overall yield using known procedure[16] (Scheme 1). The S_N2' coupling reaction of benzylmagnesium bromide with **14** furnished the diester **15** in 70% yield, with an *exo* carbon–carbon double bond. Lithium hydroxide hydrolysis of diester **15** at room temperature, followed by acidification with hydrochloric acid gave the desired dicarboxylic acid **16** in 92% yield, without isomerization of carbon–carbon double bond. The addition of molecular bromine to the carbon–carbon double bond in **16** gave a mixture of all possible isomers of dibromodicarboxylic acid **17** in ~100% yield. The dibromodicarboxylic acid **17** underwent a very smooth in situ dehydration followed by dehydrobromination reaction in presence of acetic anhydride at reflux to give unsymmetrical (bromomethyl)benzylmaleic anhydride (**19**) in ~100% yield via the unisolable intermediate dibromosuccinic anhydride **18**. The chemoselective allylic substitution of the bromide in anhydride **19** with phenylmagnesium bromide furnished dibenzylmaleic anhydride (**20**) in 45% yield. Sodium borohydride reduction



Scheme 1. Reagents, conditions and yields: (i) $PhCH_2MgBr$ (1.5 equiv), THF, HMPA, −20 °C, 0.5 h (70%); (ii) (a) LiOH (10 equiv), THF+H_2O (3:1), rt, 18 h, (b) H^+/HCl (92%); (iii) Br_2 (1.5 equiv), CCl_4, rt, 6 h (~100%); (iv) Ac_2O, reflux, 1.5 h (~100%); (v) C_6H_5MgBr (5 equiv) CuI (0.1 equiv), Et_2O, HMPA, −5 to 0 °C (45%); (vi) $NaBH_4$ (2.5 equiv), THF, 0 °C, 2 h (91%); (vii) Piperidine (0.7 equiv), PhCHO (1 equiv), MeOH, rt, 16 h (77%); (viii) $CHCl_3$, rt, 8 days (50%); (ix) H_2, Pd/C, EtOAc, 12 h (75%); (x) △, 200 °C, 3 h (100%).



Scheme 2. Reagents, conditions and yields: (i) C_3H_7MgBr (1.5 equiv), THF, HMPA, −20 °C, 0.5 h (79%); (ii) (a) LiOH (10 equiv), THF+H_2O (3:1), rt, 18 h, (b) H^+/HCl (91%); (iii) Br_2 (1.5 equiv), CCl_4, rt, 6 h (~100%); (iv) Ac_2O, reflux, 1.5 h (~100%); (v) C_6H_5MgBr (5 equiv), CuI (0.1 equiv), Et_2O, HMPA, −5 to 0 °C (43%); (vi) $NaBH_4$ (2.5 equiv), THF, 0 °C, 4 h (70%).

of dibenzylmaleic anhydride (**20**) in THF at room temperature gave the desired lactone **21** in 91% yield. The Knoevenagel condensation of lactone **21** with benzaldehyde furnished the naturally occurring maculalactone B (**1**) in 77% yield. The maculalactone B (**1**) on palladium–charcoal catalyzed chemoselective hydrogenation gave the (±)-maculalactone A (**3**) in 75% yield. The photochemical conversion of maculalactone B (**1**) to the maculalactone C (**2**) is known in 80% yield.[12] The maculalactone B (**1**) is thermodynamically more stable than the maculalactone C (**2**), but due to the presence of associated π-stacking interaction between the two phenyl groups,[2] it slowly transforms to maculalactone C (**2**). The maculalactone B (**1**) in chloroform at room temperature underwent nearly 50% conversion to maculalactone C (**2**) in 8 days (by ^{1}H NMR). We isolated and heated the neat 50:50 mixture of maculalactones B and C at 200 °C for 3 h and obtained exclusively the maculalactone B (**1**) proving that it is thermodynamically more stable than maculalactone C (**2**). The maculalactones B plus C mixture on catalytic hydrogenation also gave the maculalactone A (**3**) in same 75% yield. The analytical and spectral data obtained for maculalactones A–C were in complete agreement with reported data.[2,12]

Our next plan was to design the bioactive natural product nostoclide I (**4**). Starting from diester **14**, we similarly prepared the benzylisopropylmaleic anhydride (**27**) in 5-steps with 20% overall yield via S_N2' Grignard coupling, hydrolysis, bromination, in situ dehydration followed by dehydrobromination and allylic substitution pathway (Scheme 2). The sodium borohydride induced regioselective reduction of unsymmetrical maleic anhydride **27** in THF at 0 °C gave the separable mixture of desired and undesired lactones **29** and **28** with 70% yield in 3:2 ratio, respectively. The analytical and spectral data obtained for lactone **29** was in complete agreement with reported data. The conversion of lactone **29** to nostoclide I (**4**) is well known in the literature.[13]

3. Conclusion

In summary, starting from readily available citraconic anhydride we have demonstrated the multi-step synthesis of novel bioactive natural products maculalactone A (10-steps, 10%), maculalactone B (9-steps, 13%), maculalactone C (10-steps, 7%) via the three different types of carbon–carbon coupling reactions. In the synthesis of these unusual natural products with three phenyl rings, the first phenyl ring unit was loaded by S_N2' Grignard reaction, the second phenyl ring was coupled via allylic substitution reaction, while the third phenyl ring unit was attached using Knoevenagel condensation reaction. Similarly, we have also completed the formal synthesis of bioactive natural product nostoclide I (**4**), the desired precursor **29** was obtained in 8-steps with 14% overall yield. We feel that our present approach is general in nature and can be used to design diverse butyrolactone skeletons for the structure–activity relationship studies.

4. Experimental

4.1. General

Melting points are uncorrected. The ^{1}H NMR spectra were recorded on Bruker AC 200 NMR spectrometer and Bruker MSL 300 NMR spectrometer with TMS as an internal standard. The ^{13}C NMR spectra were recorded on Bruker AC 200 NMR spectrometer (50 MHz) and Bruker MSL 300 NMR spectrometer (75 MHz). IR spectra were recorded on Shimadzu FTIR instrument. Microanalytical data were obtained using a Carlo-Erba CHNS-O EA 1108 elemental analyzer. Column chromatographic separations were carried out on silica gel (60–120 mesh) and flash chromatographic separation was carried out using 230–400 mesh size silica gel. Commercially available citraconic anhydride, benzyl bromide, 2-bromopropane, bromobenzene, magnesium turnings, HMPA, CuI, lithium hydroxide, piperidine, acetic anhydride, $NaBH_4$ and benzaldehyde were used.

4.1.1. Dimethyl 1-buten-4-phenyl-2,3-dicarboxylate (15). A fresh solution of benzylmagnesium bromide in ether was prepared as follows. A solution of benzyl bromide (4.10 g, 24 mmol) in LAH–dried ether (20 mL) was added at room temperature to magnesium turnings (1.73 g, 72 mmol) in ether (20 mL) under argon with constant stirring in three equal portions at an interval of 10 min. The reaction mixture was stirred at room temperature for a further 4 h. This freshly generated Grignard reagent was added drop wise to a solution of HMPA (14.34 g, 80 mmol) and **14** (3.79 g, 16 mmol) in anhydrous ether (40 mL) under argon at −20 °C and the reaction mixture was stirred at the same temperature for a further 30 min. The reaction was quenched by the addition of a saturated ammonium chloride solution (50 mL). An additional quantity of ether (50 mL) was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with ether (30 mL×3), the combined ether extract was washed with water and brine, dried with Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether/ethyl acetate (9.5:0.5) to give **15**: 2.78 g (70% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.96 (dd, J=14, 6 Hz, 1H), 3.25 (dd, J=14, 8 Hz, 1H), 3.63 (s, 3H), 3.76 (s, 3H), 3.75–3.90 (m, 1H), 5.67 (s, 1H), 6.31 (s, 1H), 7.10–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.3, 48.6, 51.9, 52.0, 126.3, 127.3, 128.2, 128.8, 137.5, 138.6, 166.2, 172.8; IR ($CHCl_3$) ν_{max} 1730, 1725, 1630 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.81; H, 6.44.

4.1.2. Dimethyl 1-penten-4-methyl-2,3-dicarboxylate (22). Repetition of above procedure using 2-propylmagnesium bromide (prepared from 2-bromopropane (2.95 g, 24 mmol) and magnesium (1.73 g, 72 mmol)) and **14** (3.79 g, 16 mmol) gave the corresponding diester **22**: 2.53 g (79% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (d, J=7 Hz, 3H), 0.97 (d, J=7 Hz, 3H), 2.10–2.50 (m, 1H), 3.41 (d, J=10 Hz, 1H), 3.66 (s, 3H), 3.76 (s, 3H), 5.92 (s, 1H), 6.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.8, 20.7, 31.2, 51.4, 51.9, 52.3, 127.0, 137.6, 166.8, 173.3; IR (neat) ν_{max} 2961, 1736, 1726, 1626 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 59.93; H, 8.11.

4.1.3. 1-Buten-4-phenyl-2,3-dicarboxylic acid (16). A solution of lithium hydroxide (2.40 g in 18 mL water) was added to a solution of **15** (2.48 g, 10 mmol) in tetrahydrofuran (54 mL) at room temperature and the reaction mixture was stirred for 18 h. The reaction mixture was then concentrated in vacuo. To the residue was added ethyl acetate (100 mL) and then acidified to pH 2 with 2 M hydrochloric acid. The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (30 mL×3). The combined organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether/ethyl acetate (6:4) to give **16**: 2.02 g (92% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.03 (dd, J=14, 10 Hz, 1H), 3.38 (dd, J=14, 6 Hz, 1H), 3.60–3.75 (m, 1H), 5.61 (s, 1H), 6.42 (s, 1H), 7.00–7.40 (m, 5H), 10.6 (bs, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 36.6, 48.8, 126.6, 128.5, 128.9, 131.0, 136.4, 138.3, 171.7, 179.0; IR (Nujol) ν_{max} 2700–2500, 1709, 1705, 1628 cm^{-1}. Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.52; H, 5.43.

4.1.4. 1-Penten-4-methyl-2,3-dicarboxylic acid (23). It was prepared similarly from **22** (2.00 g, 10 mmol) and aqueous lithium hydroxide solution (2.40 g in 18 mL water) as described above to obtain the corresponding dicarboxylic acid **23**: 1.57 g (91% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.92 (d, J=6 Hz, 3H), 1.06 (d, J=6 Hz, 3H), 2.05–2.35 (m, 1H), 3.40 (d, J=10 Hz, 1H), 6.07 (s, 1H), 6.62 (s, 1H), 10.16 (bs, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.9, 20.8, 31.1, 52.3, 130.3, 136.7, 172.0, 179.3; IR ($CHCl_3$) ν_{max} 3020, 2968, 2700–2500, 1703, 1701, 1624 cm^{-1}. Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.73; H, 7.00.

4.1.5. 1,2-Dibromobutan-4-phenyl-2,3-dicarboxylic acid (17). A solution of bromine (1.92 g, 12 mmol) in CCl_4 (20 mL) was added dropwise to a solution of **16** (1.76 g, 8 mmol) in CCl_4 (30 mL) at room temperature and the reaction mixture was stirred for 6 h. The reaction mixture was then concentrated in vacuo, and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with saturated sodium metabisulphite, water and brine, dried over Na_2SO_4 and concentrated in vacuo, to obtain **17**: 3.03 g (∼100% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.00–3.40 (m, 2H), 3.64 (t, J=6 Hz, 1H), 3.85–4.25 (m, 2H), 7.00–7.60 (m, 5H), 11.01 (bs, 2H); IR (Nujol) ν_{max} 2700–2500, 1757, 1713, 1605 cm^{-1}. Anal. Calcd for $C_{12}H_{12}Br_2O_4$: C, 37.93; H, 3.18. Found: C, 37.97; H, 3.11.

4.1.6. 1,2-Dibromopentan-4-methyl-2,3-dicarboxylic acid (24). It was prepared similarly from **23** (1.38 g, 8 mmol) and bromine (1.92 g, 12 mmol) as described above to obtain the corresponding diacid **24**: 2.65 g (∼100% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80–1.40 (m, 6H), 2.00–2.45 (m, 1H), 3.30–3.55 (m, 1H), 3.80–4.50 (m, 2H), 8.76 (bs, 2H); IR ($CHCl_3$) ν_{max} 1714, 1711 cm^{-1}. Anal. Calcd for $C_8H_{12}Br_2O_4$: C, 28.94; H, 3.64. Found: C, 29.01; H, 3.66.

4.1.7. 2-Bromomethyl-3-benzylmaleic anhydride (19). A solution of **17** (3.03 g, 8 mmol) in acetic anhydride (20 mL) was gently heated at reflux for 1.5 h and the reaction mixture was concentrated under vacuo at 50 °C. The residue was diluted with ethyl acetate (40 mL) and the organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated in vacuo to obatin **19**: 2.24 g (∼100% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.91 (s, 2H), 4.05 (s, 2H), 7.15–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.9, 30.7, 127.6, 128.9, 129.1, 133.6, 139.0, 144.7, 163.6, 164.6; IR ($CHCl_3$) ν_{max} 1828, 1773, 1705, 1638 cm^{-1}. Anal. Calcd for $C_{12}H_9BrO_3$: C, 51.27; H, 3.23. Found: C, 51.33; H, 3.18.

4.1.8. 2-Bromomethyl-3-isopropylmaleic anhydride (26). It was prepared similarly from **24** (2.65 g, 8 mmol) and acetic anhydride (20 mL) as described above to obtain the corresponding anhydride **26**: 1.86 g (∼100% yield); thick oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (d, J=9 Hz, 6H), 3.09 (sept, J=9 Hz, 1H), 4.21 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.8, 19.5, 26.7, 137.7, 151.2, 163.6, 163.7; IR ($CHCl_3$) ν_{max} 1850, 1832, 1773, 1707, 1655 cm^{-1}. Anal. Calcd for $C_8H_9BrO_3$: C, 41.23; H, 3.89. Found: C, 41.17; H, 3.85.

4.1.9. 2,3-Dibenzylmaleic anhydride (20). A fresh solution of phenylmagnesium bromide in ether was prepared as follows. A solution of bromobenzene (3.93 g, 25 mmol) in LAH–dried ether (20 mL) was added at room temperature to magnesium turnings (1.80 g, 75 mmol) in ether (20 mL) under argon with constant stirring in three equal portions at an interval of 10 min. The reaction mixture was stirred at room temperature for a further 4 h. This freshly generated Grignard reagent was added dropwise to a solution of **19** (1.41 g, 5 mmol) and copper (I) iodide (95 mg, 0.5 mmol) in ether (30 mL) and HMPA (10 mL) under argon at −5 to 0 °C over 15–20 min with stirring. The reaction mixture was allowed to reach room temperature and stirred for a further 8 h. It was diluted with ether (30 mL) and acidified with 4 M H_2SO_4 (30 mL), and the aqueous layer was further extracted with ether (30 mL×3). The combined organic layer was washed with water, brine and dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed over silica gel using petroleum ether/ethyl acetate (9.5:0.5) to give **20**: 626 mg (45% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.78 (s, 4H), 7.05–7.20 (m, 4H), 7.20–7.35 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.9, 127.1, 128.6, 128.8, 134.9, 142.7, 165.6; IR ($CHCl_3$) ν_{max} 1769 cm^{-1}. Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.75; H, 5.14.

4.1.10. 2-Benzyl-3-isopropylmaleic anhydride (27). Repetition of above procedure using phenylmagnesium bromide (prepared from bromobenzene (3.93 g, 25 mmol) and magnesium (1.80 g, 75 mmol)), **26** (1.17 g, 5 mmol), copper (I) iodide (95 mg, 0.5 mmol) and HMPA (10 mL) gave the corresponding anhydride **27**: 495 mg (43% yield); thick oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28 (d, J=9 Hz, 6H), 3.06 (sept, J=9 Hz, 1H), 3.81 (s, 2H), 7.15–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.0, 26.4, 29.8, 126.2, 127.3, 127.9, 128.6, 129.0, 135.7, 141.2, 149.1, 164.4, 165.8; IR (neat) ν_{max} 1773, 1703, 1605 cm^{-1}. Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.96; H, 6.07.

4.1.11. 3,4-Dibenzyl-5*H*-furan-2-one (21). To a stirred solution of **20** (300 mg, 1.08 mmol) in THF, $NaBH_4$ (102 mg, 2.70 mmol) was added at 0 °C and the reaction mixture was further stirred at 0 °C for 2 h and then quenched with water and acidified with dilute HCl and extracted with ethyl acetate (50 mL×3). The organic layer was washed with brine, dried with Na_2SO_4, concentrated in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:4) to furnish **21**: 259 mg (91% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.72 (s, 2H), 3.74 (s, 2H), 4.53 (s, 2H), 6.95–7.10 (m, 2H), 7.15–7.50 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.6, 33.5, 71.2, 126.6, 126.8, 127.2, 128.6, 128.7, 129.0, 130.1, 135.8, 138.0, 159.7, 174.6; IR ($CHCl_3$) ν_{max} 1755, 1672, 1601 cm^{-1}. Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.83; H, 6.05.

4.1.12. 3-Isopropyl-4-benzyl-5*H*-furan-2-one (28) and 3-benzyl-4-isopropyl-5*H*-furan-2-one (29). Repetition of above procedure using **27** (248 mg, 1.08 mmol) and $NaBH_4$ (102 mg, 2.70 mmol) gave the mixture of both the corresponding lactones (**28**:**29**=40:60) 163 mg (70% yield). The mixture was separated by flash column chromatography using a mixture of ethyl acetate and petroleum ether (1:17) to furnish **28** (65 mg) and **29** (98 mg). **28**: thick oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (d, J=9 Hz, 6H), 2.97 (sept, J=9 Hz, 1H), 3.77 (s, 2H), 4.49 (s, 2H), 7.15 (dd, J=9, 3 Hz, 2H), 7.25–7.45 (m, 3H); IR ($CHCl_3$) ν_{max} 1746, 1665, 1603 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.67; H, 7.52.

29: thick oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.11 (d, J=9 Hz, 6H), 3.08 (sept, J=9 Hz, 1H), 3.63 (s, 2H), 4.73 (s, 2H), 7.10–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.9, 27.3, 29.4, 68.7, 124.5, 126.5, 128.4, 128.6, 138.2, 166.9, 175.1; IR ($CHCl_3$) ν_{max} 1753, 1666, 1603 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.81; H, 7.53.

4.1.13. 3,4-Dibenzyl-5*Z*-benzylidine-5*H*-furan-2-one (maculalactone B, 1). To a stirred solution of lactone **21** (200 mg, 0.76 mmol) in methanol, piperidine (0.05 mL, 0.53 mmol) and benzaldehyde (0.08 mL, 0.76 mmol) were added at room temperature and the reaction mixture was stirred for another 15 h. Removal of solvent in vacuo followed by column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (1:9) furnished **1**: 206 mg (77% yield); mp=102–103 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.74 (s, 2H), 3.93 (s, 2H), 5.97 (s, 1H), 7.05–7.40 (m, 13H), 7.71 (dd, J=6, 2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.8, 30.6, 110.4, 126.7, 127.0, 127.7, 127.9, 128.2, 128.4, 128.6, 128.7, 128.8, 128.9, 129.3, 130.5, 133.1, 136.6, 137.5, 148.3, 150.7, 170.2; IR ($CHCl_3$) ν_{max} 1755, 1649, 1603 cm^{-1}. Anal. Calcd for $C_{25}H_{20}O_2$: C, 85.20; H, 5.72. Found: C, 85.27; H, 5.66.

4.1.14. 3,4-Dibenzyl-5*E*-benzylidine-5*H*-furan-2-one (maculalactone C, 2). A solution of **1** (100 mg) in $CHCl_3$ (10 mL) was kept at room temperature for 8 days. Concentration of above $CHCl_3$ solution in vacuo furnished 100 mg of 50:50 mixture of **1** and **2**. In ^{1}H NMR ($CDCl_3$), the vinylic proton in **2** appeared at δ 6.84. The preparative HPLC separation of mixture of **1** and **2** is known.[12]

4.1.15. 3,4,5-Tribenzyl-5*H*-furan-2-one (maculalactone A, 3). A mixture of **1** (100 mg, 0.28 mmol) and a catalytic amount of Pd/C in ethyl acetate (8 mL) was subjected to hydrogenation at 65-psi hydrogen pressure for 16 h at room temperature. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:4) to furnish **3**: 75 mg (75% yield); thick oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.82 (dd, J=12, 6 Hz, 1H), 3.23 (dd, J=12, 3 Hz, 1H), 3.48 (d, J=15 Hz, 1H), 3.57 (d, J=15 Hz, 1H), 3.64 (d, J=15 Hz, 1H), 3.92 (d, J=15 Hz, 1H), 4.94 (dd, J=6, 3 Hz, 1H), 6.88 (m, 2H), 7.02 (m, 2H), 7.05–7.40 (m, 11H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.3, 33.1, 37.9, 81.5, 126.3, 127.1, 127.3, 128.1, 128.5 (3-carbons), 128.6, 129.0, 129.4, 134.8, 135.9, 137.6, 161.7, 173.5; IR (neat) ν_{max} 1755, 1668, 1603 cm^{-1}. Anal. Calcd for $C_{25}H_{22}O_2$: C, 81.06; H, 5.98. Found: C, 80.93; H, 5.86.

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