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Graphical Abstract

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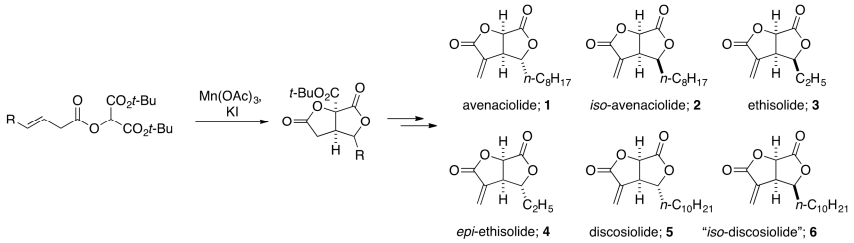

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ABSTRACT

The avenaciolide family of natural products are small α-methylene bis-γ-lactones that exhibit a wide variety of biological activities. Herein we report concise syntheses of five members of this family of natural products along with the synthesis of one non-natural analogue. The syntheses proceed in five or six steps from simple, commercially available compounds and feature a key oxidative cyclization/lactonization reaction that likely occurs *via* a radical mechanism.

1. Introduction

The α-methylene-γ-lactone moiety is prevalent in a wide variety of structurally diverse biologically active natural products that have attracted the attention of synthetic chemists since the middle of the 20th century.[1-4] A small sub-set of these natural products that have garnered considerable synthetic attention are the avenaciolides, ethisolides and discosiolide (Figure 1).[5] These small natural products all consist of an α-methylene-γ-lactone *cis*-fused to a second γ-lactone and differ in the configuration and nature of the C-4 alkyl substituent.

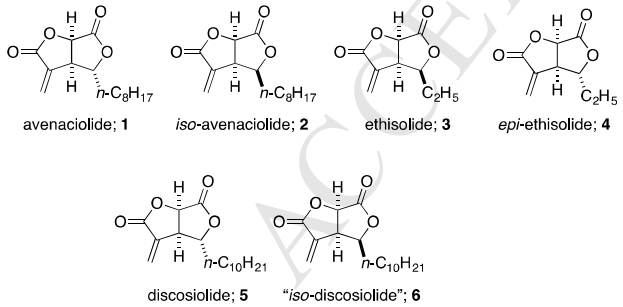
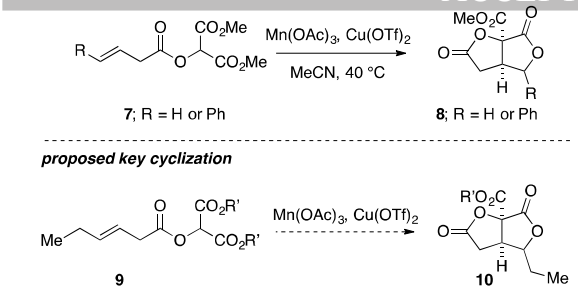


Figure 1. α-Methylene-γ-lactone natural products of the avenaciolide family.

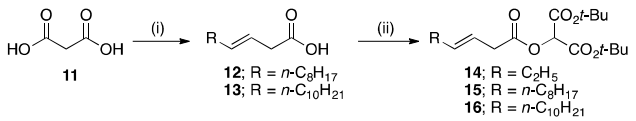
The first member of this family of natural products to be reported was avenaciolide **1** isolated from a strain of *Aspergillus avenaceus*.[6-7] Its structure was determined by a combination of chemical degradation and NMR methods[6] and later by single crystal X-ray analysis.[8] A few years later *iso*-avenaciolide **2** was isolated from a large-scale growth of *Aspergillus avenaceus*[9] and determined to be the C-4 diastereomer of avenaciolide. At the same time ethisolide **3** was isolated from an unidentified *Penicillium* species and its structure determined by spectroscopic/spectrometric methods and by comparison with the data of avenaciolide **1** and *iso*-avenaciolide **2**.[9-10] In 1994 *epi*-ethisolide **4** and discosiolide **5** were isolated from fungal extracts.[11] Given that avenaciolide **1** and *iso*-avenaciolide **2**, and ethisolide **3** and *epi*-ethisolide **4** are C-4 epimers, it is not unreasonable to propose that "*iso*-discosiolide" **6** may be a yet-to-be-isolated natural product. The natural products **1-5** display a wide variety of biological activities including antifungal,[6, 11] antibacterial[12] and herbicidal activity.[11] Furthermore inhibition of glutamate transport in rat mitochondria[13] as well as inhibition of a human dual-specificity phosphatase have been reported.[14] Given their compact structures and wide-ranging biological activities these small natural products have been the subject of numerous total syntheses.[15] Recently we reported the oxidative radical cyclization of unsaturated ester malonates which gave the corresponding bis-lactones in good yield and with good levels of diastereocontrol (**7**→**8**, Scheme 1).[16] We reasoned that if we could extend the substrate scope of this reaction to alkyl substituted alkenes such as **9** then the product bis-lactone **10** would be readily converted into the corresponding natural products (in this case **3** and/or **4)** in only a few steps. In the event, the key cyclization/lactonization required the development of new methodology (*vide infra*).



Scheme 1. Oxidative radical cyclization to form bis-lactones.

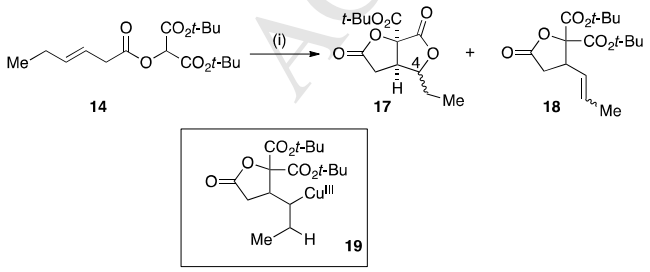
2. Results and Discussion

In order to explore the proposed key cyclization an efficient synthesis of the cyclization substrate(s) was required. The ester malonates required for the synthesis of the natural products were all prepared from the di-*t*-butyl diazomalonate and the corresponding β,γ-unsaturated acids under rhodium(II) catalysis.[16] *trans*-3-Hexenoic acid is commercially available and the other β,γ-unsaturated acids **12** and **13** were readily synthesized through a Knoevenagel condensation / decarboxylation sequence between malonic acid **11** and the corresponding aliphatic aldehydes.[17] The full synthetic sequence is shown in Scheme 2.



Scheme 2. Cyclization substrate synthesis. (i) *n*-decanal or *n*-dodecanal, *N*-methylmorpholine, 80 °C, 7 h, **12** 91%, **13** 92%; (ii) di-*t*-butyl diazomalonate with **12**, **13**, or *trans*-3-hexenoic acid, $Rh_2(OAc)_4$, benzene, 60 °C, **14** 78%, **15** 81%, **16** 88%.

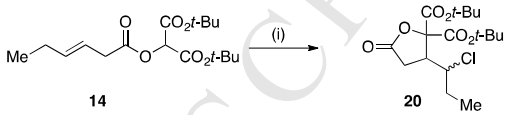
Having secured efficient syntheses of the cyclization substrates we moved to investigate the oxidative radical cyclization. Despite the use of manganese(III) acetate in conjunction with a variety of copper(II) salts for the synthesis of γ-lactones, in general γ-lactones are only formed in good yields from terminal alkene or styrene substrates such as **7** and there have been few reports of the use of alkyl-substituted alkenes giving good yields of γ-lactones.[16, 18-22] In the event, exposure of the malonate **14** to manganese(III) acetate and copper(II) triflate, according to our previous work, gave the corresponding bis-lactone **17** in 24% yield as a 1.2:1 mixture of C-4 diastereomers[23] along with the corresponding alkene **18** in 40% yield as a 3.8:1 mixture of (*E*):(*Z*)-diastereomers (Scheme 3).



Scheme 3. Oxidative radical cyclization. (i) $Mn(OAc)_3$, $Cu(OTf)_2$, MeCN, 40 °C, **17** 24% (1.2:1 mixture of C-4 diastereomers), **18** 40% (3.8:1 mixture of (*E*):(*Z*) diastereomers).

Unfortunately, all attempts to significantly improve the yield of the lactone by modification of the malonate ester (*t*-Bu, Et, Me) substrate (e.g. **14**, **15** or **16**), or the copper(II) source met with failure and the corresponding alkenes were always formed as the major product with the desired bis-lactones formed as the minor products. The likely reason for this is that the proposed secondary copper(III) intermediate **19** more readily undergoes β-hydride elimination than lactonization in keeping with previous reports from Snider.[24]

Using our previously developed methodology, we had only been able to gain access to the required bis-lactones **17** in low yields. Aware that additives can greatly influence the outcome of manganese(III) acetate-mediated reactions, we elected to investigate the use of halide salts in these reactions.[25] Much to our delight addition of lithium chloride to our standard reaction conditions gave the chlorolactone **20** in 80% yield[25] as a 3.3:1 mixture of (unassigned) diastereomers without any alkene being formed (Scheme 4).



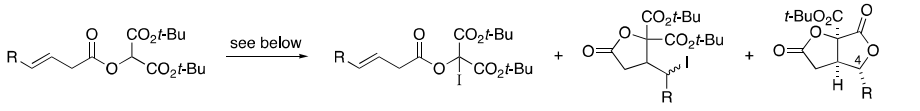
Scheme 4. Formation of the chlorolactones **20**. (i) $Mn(OAc)_3$, $Cu(OTf)_2$, MeCN, LiCl, 40 °C, 80% (3.3:1 mixture of unassigned diastereomers).

Unfortunately, we were unable to convert this chlorolactone into the desired bis-lactone **17** in reasonable yield under a number of conditions. The poor results from the attempted lactonization reaction most likely arises from the relatively strong C–Cl bond (397 $kJmol^{-1}$) that renders the chloride an ineffective leaving group. We therefore moved to the use of iodide as an additive with a view to the formation of the corresponding iodides from which the bis-lactones should be more readily formed (C–I bond strength, 209 $kJmol^{-1}$). However, we were aware that the low reduction potential of iodine ($E_{1/2}^{0/-I}$ = +0.535 V) and the oxidizing ability of manganese(III) acetate ($E_{1/2}^{III/II}$ = +1.51 V) might render this combination of reagents ineffective for the desired transformation.

In the event, addition of potassium iodide to our standard reaction conditions of manganese(III) acetate and copper(II) triflate in acetonitrile at 40 °C using substrate **14**, gave a mixture of three compounds by crude ^{1}H NMR analysis – the bis-lactone **17**, the iodo-lactone **26** and the iodomalonate **22** in approximately a 1:1.6:1 ratio (Table 1, entry 1); the iodo-lactone **26** and the bis-lactone **17** were fully characterized after purification by flash chromatography; the identity of the iodomalonate **22** was inferred from analysis of the crude ^{1}H NMR. The same reaction was performed at 60 °C on the terminal alkene **21**, prepared in an analogous manner to compounds (**14**-**16**), which yielded only the corresponding iodo-lactone **29** and bis-lactone **32** in 41% and 12% isolated yields respectively (Table 1, entry 2). Increasing the temperature of the reaction to 80 °C using substrate **14** resulted in exclusive formation of the bis-lactone **17** in 74% yield (Table 1, entry 3), while using substrates **15** and **16** gave only the corresponding bis-lactones **30** and **31** in 57% and 53% yields respectively with the iodomalonates **23** and **24** and iodolactones **27** and **28** not being observed (Table 1, entries 4 and 5). Using substrate **14** and reducing the reaction time had a deleterious effect on the yield of the bis-lactone product **17** with the iodolactones **26** being formed in 21% yield (Table 1, entry 6); conducting the reaction in an open-flask exposed to air was also deleterious to the yield of the bis-lactones **17** (Table 1, entry 7). Control experiments indicated the copper(II) salt was not required. Using manganese(III)

acetate and sub-stoichiometric quantities of KI gave cleaner reactions than with the addition of copper(II) salts, with the bis-lactone **17** being formed in 78% NMR yield as a 3:1 mixture with the starting material (Table 1, entry 8). Increasing

Table 1. Cyclizations using manganese(III) acetate and potassium iodide.



14; R = C_2H_5
15; R = *n*-C_8H_{17}
16; R = *n*-$C_{10}H_{21}$
21; R = H

22; R = C_2H_5
23; R = *n*-C_8H_{17}
24; R = *n*-$C_{10}H_{21}$
25; R = H

26; R = C_2H_5
27; R = *n*-C_8H_{17}
28; R = *n*-$C_{10}H_{21}$
29; R = H

17; R = C_2H_5
30; R = *n*-C_8H_{17}
31; R = *n*-$C_{10}H_{21}$
32; R = H

Entry[a, b]	R	Additive 1	Additive 2	T / °C	iodomalonate / %	iodolactone / %[c]	bis-lactone /%[d]
1	C_2H_5	1 equiv. $Cu(OTf)_2$	1.5 equiv. KI	40	28	41	25
2	H	1 equiv. $Cu(OTf)_2$	1.5 equiv. KI	60	trace	41	12
3	C_2H_5	1 equiv. $Cu(OTf)_2$	1.5 equiv. KI	80	-	-	74
4	*n*-C_8H_{17}	1 equiv. $Cu(OTf)_2$	1.5 equiv. KI	80	-	-	57
5	*n*-$C_{10}H_{21}$	1 equiv. $Cu(OTf)_2$	1.5 equiv. KI	80	-	-	53
6[e]	C_2H_5	1 equiv. $Cu(OTf)_2$	1.5 equiv. KI	80	-	21	53
7[f,g]	C_2H_5	1 equiv. $Cu(OTf)_2$	1.5 equiv. KI	80	-	-	46
8	C_2H_5	-	0.5 equiv. KI	80	-	-	78[h]
9[i]	**C_2H_5**	**-**	**0.5 equiv. KI**	**80**	**-**	**-**	**77**[j]
10[i]	C_2H_5	-	0.2 equiv. KI	80	-	-	63
11[i]	***n*-C_8H_{17}**	**-**	**0.5 equiv. KI**	**80**	**-**	**-**	**72**[k]
12[i]	***n*-$C_{10}H_{21}$**	**-**	**0.5 equiv. KI**	**80**	**-**	**-**	**74**[l]

[a]$Mn(OAc)_3$ (2 equiv), degassed MeCN (0.15 M) under N_2, 19 h.

[b]Distribution of products determined by ^1H NMR.

[c]Isolated as a mixture of unassigned diastereomers.

[d]Isolated as a mixture of C-4 diastereomers, major diastereomer shown.

[e]Reaction time of 2.5 h.

[f]Open-flask reaction.

[g]Reaction time of 3.5 h.

[h]Yield from ^1H NMR, **17**:**14**, 3:1.

[i]3 equiv. $Mn(OAc)_3$.

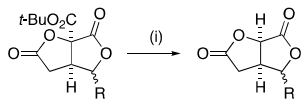
[j]Isolated as a 2.8:1 inseparable mixture of diastereomers.

[k]Isolated as a 2.3:1 inseparable mixture of diastereomers.

[l]Isolated as a 1.7:1 inseparable mixture of diastereomers.

the equivalents of manganese(III) acetate from two to three increased the isolated yield of the desired bis-lactone to 77% (Table 1, entry 9); reduction in the iodide stoichiometry led to reduction in the isolated yield of the bis-lactone to 63% (Table 1, entry 10). The optimized conditions (Table 1, entry 9) were fully transferable to substrates **15** and **16** with the corresponding bis-lactones **30** and **31** being isolated in 72% and 74% yields respectively (Table 1, entries 11 and 12). Under the optimized conditions, the bis-lactones **17**, **30** and **31** were isolated as 1.7:1 to 2.8:1 mixtures of C-4 diastereomers. In general, such low diastereoselectivities would not be synthetically useful; however, in this case, we are targeting natural products which differ only in their C-4 configuration and hence such low diastereocontrol is, in fact, an advantage.

Having developed a method that allowed the synthesis of the key bicyclic bis-lactones **17**, **30** and **31** in 2 or 3 steps from commercial materials, we then proceeded to convert them into the corresponding natural products. In order to complete the syntheses of the natural products an efficient decarboxylation/methylenation sequence needed to be developed on the bis-lactones **17**, **30** and **31**. After some optimization, it was found that Krapcho decarboxylation of the bis-lactones could be readily achieved on heating **17**, **30** and **31** with lithium chloride in DMSO and water at 160 °C for 1 hour.[26] The resulting dealkoxycarbonylated lactones **33**, **34** and **35** were isolated in 77-96% yields (Scheme 5).

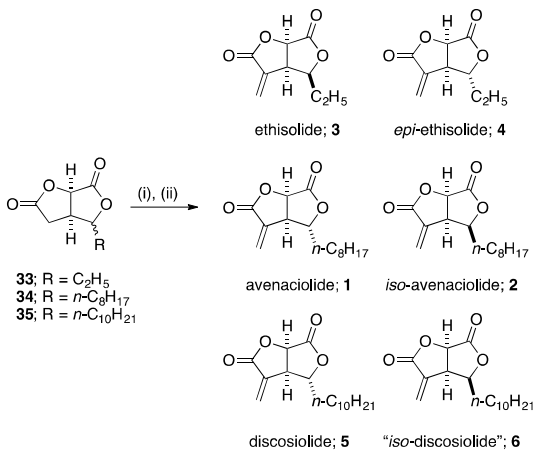


17; R = C_2H_5
30; R = *n*-C_8H_{17}
31; R = *n*-$C_{10}H_{21}$

33; R = C_2H_5
34; R = *n*-C_8H_{17}
35; R = *n*-$C_{10}H_{21}$

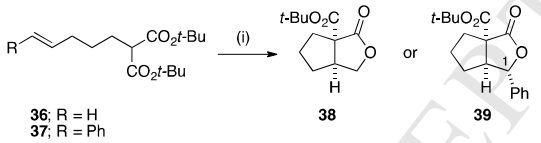
Scheme 5. Krapcho decarboxylation. (i) LiCl, DMSO, water, 160 °C, 1 h; **33**, 80%; **34**, 77%, **35**, 96%.

All that remained for the completion of the syntheses was the installation of the *exo*-methylene group. We elected to use Johnson's protocol for this transformation which involved carboxylation of the bis-lactones **33**, **34** and **35** followed by decarboxylative methylenation (Scheme 6).[15a] This procedure gave the corresponding α-methylene γ-lactones as separable mixtures of C-4 diastereomers. Specifically, ethisolide **3** and *epi*-ethisolide **4** were isolated in 18% and 34% yields respectively, avenaciolide **1** and *iso*-avenaciolide **2** in 34% and 26% yields respectively, and discosiolide 5 and '*iso*-discosiolide' **6** and in 28% and 10% yields respectively.



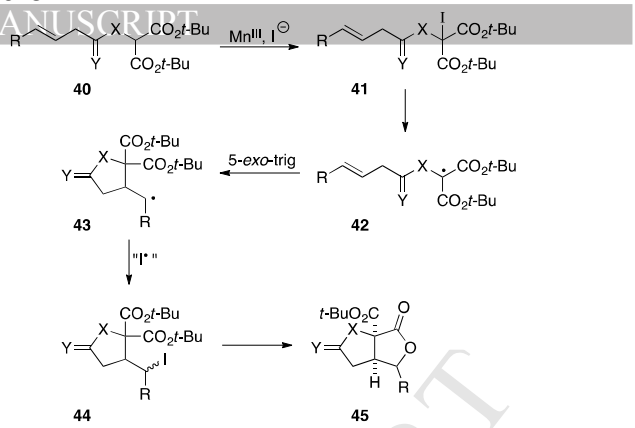
Scheme 6. Synthesis of the natural products. (i) $CH_3OMgOCO_2CH_3$ (Stile's reagent), DMF, 120 °C; (ii) H_2CO, H_2O, Et_2NH, NaOAc, AcOH, RT then 100 °C; **3** 18%, **4** 34%; **1** 34%, **2** 26%; **5** 28%, **6** 10%.

The syntheses of these natural products proceed in five or six steps from commercially available materials using a manganese(III) acetate / potassium iodide mediated cyclization/lactonization as a key step. This oxidative cyclization was also applicable to the all carbon series. Thus, exposure of the terminal- or phenyl-substituted alkenes (**36** or **37**) to manganese(III) acetate and potassium iodide gave the corresponding [3.3.0]-bicyclic γ-lactones **38** and **39** in 46% and 88% yields respectively (Scheme 7).



Scheme 7. Synthesis of carbocyclic products. (i) $Mn(OAc)_3$, KI, MeCN, 80 °C, 21 h; **38** 46%; **39** 88% (9:1 mixture of C-1 diastereomers, major diastereomer shown).

Taking into consideration Curran's work on atom transfer radical cyclization reactions,[27-28] along with the results from the above cyclization reactions which include the isolation of the iodolactones **26** and **29**, we propose that the mechanism of the reaction proceeds according to that depicted in Scheme 8. Thus, the malonate substrates **40** are converted into the corresponding iodomalonates **41** on exposure to Mn(III) and potassium iodide. The iodomalonates **41** then undergo thermal or metal-mediated atom transfer radical cyclization *via* the malonyl radicals **42** to give the adduct radicals **43**. The adduct radicals are then converted into the corresponding iodides **44** by reaction with an iodine atom source which is likely to be either molecular iodine, formed from the oxidation of iodide by Mn(III), or by iodine atom transfer from the substrates **41**. Thermal lactonization then delivers the products **45** and regenerates iodide.[29]



Scheme 8. Plausible mechanism of the oxidative lactonization reaction. X = Y = O or X = CH_2, Y = H_2.

3. Conclusions

In conclusion, we have developed short syntheses of the natural products avenaciolide **1** and *iso*-avenaciolide **2**, ethisolide **3** and *epi*-ethisolide **4,** and discosiolide **5**, and of the non-natural product that we have named *iso*-discosiolide **6**, using an oxidative cyclization/lactonization as a key step. Further application of the manganese(III) acetate, potassium iodide cyclization/lactonization to natural product synthesis will be reported in due course.

4. Experimental section

^1H and ^{13}C spectra were recorded on a Bruker AVF-400 (400/100 MHz), Bruker AVH-400 (400/100 MHz) or Bruker AVG-400 (400 / 100 MHz) spectrometer. Proton (^1H) and carbon (^{13}C) chemical shifts are quoted in ppm and are internally referenced to the residual protonated solvent signal. Assignments were made on the basis of chemical shifts, coupling constants, COSY, HSQC data, relative intensities and comparison with spectra of related compounds. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintuplet), m (multiplet), dd (double doublet) and so on. Coupling constants (*J*) are measured in Hz and are rounded to the nearest 0.1 Hz.

High resolution mass spectra were recorded by the Mass Spectrometry Service at the University of Oxford Chemistry Research Laboratory using a Bruker Daltronics microTOF spectrometer (ES). Mass values (*m*/*z*) are reported in Daltons. High resolution values are calculated to at least four decimal places from the molecular formula, with all found values reported within a tolerance of 5 ppm. Low resolution mass spectra were recorded on a Fisons Platform spectrometer (ES).

Infrared spectra were recorded using a Bruker Tensor 27 Fourier Transform spectrophotometer using thin films on a diamond ATR. Absorption maxima ($\square_{max}$) are classified as strong (s), medium (m), weak (w) and broad (br) and are quoted in wavenumbers (cm^{-1}). Melting points were determined using a Leica Galen III Compound Microscope apparatus and are uncorrected.

Analytical TLC was performed on Merck DC-Alufolien 60 F254 0.2 mm precoated plates and visualized using an ultraviolet lamp, acidic vanillin or basic potassium permanganate dips. Retention factors (R_f) are reported with the solvent system used in parentheses. Flash column chromatography (FC) was

performed on Merck 60 silica (particle size 4063 μm, pore diameter 60 Å) and the solvent system used is in parentheses.

All non-aqueous reactions were carried out in oven-dried glassware sealed with a rubber septum under a positive pressure of dry nitrogen or argon from a manifold or balloon. Reactions were stirred using Teflon-coated magnetic stirrer bars. Elevated temperature reactions were maintained using a Thermowatch-controlled DrySyn™ heating block or oil bath. Reagents were purchased from commercial suppliers and used without further purification unless otherwise stated. Dry solvents were purified using standard techniques. Water used experimentally was deionized. Organic solutions were concentrated using a Büchi rotary evaporator with a water bath temperature of 30 °C. Brine refers to a saturated solution of sodium chloride in water. 'Petrol' refers to the fraction of light petroleum ether with a boiling point in the range of 40–60 °C unless otherwise stated. Compound names are generated by ChemDraw™ Professional 15.1. The relative configuration of the product [3.3.0]-bicyclic-lactones was assigned on the basis of ^{1}H NMR nOe experiments or by analogy with previous work. Where nOe data were not obtained, it was assumed that the [3.3.0]-bicyclic-lactones were cis-configured in keeping with those [3.3.0]-bicyclic-lactones for which ^{1}H NMR nOe data was readily obtained and from previous precedent.[16, 19, 30-31] Di-*t*-butyl diazomalonate was prepared according to a literature procedure.[16]

4.1. General procedure 1: Decarboxylative Knoevenagel reaction

According to the procedure reported by Zhang *et al.*,[17] a solution of malonic acid and the appropriate aldehyde in *N*-methylmorpholine (NMM, 2.3 mL) was heated to 80 °C for 7 h. Sulfuric acid 11% aqueous solution (10 mL) was added to the reaction mixture at RT and stirring was continued for 10 min. The mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the organic layers were washed with H_2O, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a colorless gel which was used without further purification.

4.2. General procedure 2: Rh-catalyzed OH insertion

According to the procedure of Chany *et. al.*[16] $Rh_2(OAc)_4$ (6 mol%) was added to a solution of alkenoic acid (1.0 eq) and di-*t*-butyl diazomalonate (1.12 eq) in benzene (0.25 M). The reaction mixture was then stirred at 60 °C for 2 h. After cooling the volatiles were removed *in vacuo* and the resulting oil was purified by FC ($PE_{40–60}$ / Et_2O).

4.3. General procedure 3: manganese(III), copper(II) potassium iodide oxidative cyclization

To a solution (0.15 M) of the alkene malonate derivative (1.0 eq, 0.15 M) in MeCN (previously sparged with Ar for 15 min) were added $Mn(OAc)_3$•$2H_2O$ (2.0 eq), $Cu(OTf)_2$ (1.0 eq) and KI (1.5 eq.). The reaction mixture was stirred at the specified temperature overnight. To the cool mixture was added sat. $Na_2S_2O_3$ (aq). The aqueous phase was extracted with EtOAc and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude was purified by FC.

4.4. General procedure 4: manganese(III), potassium iodide oxidative cyclization

To a solution of the alkene malonate derivative (1.0 eq, 0.15 M) in MeCN (previously sparged with Ar for 15 min) were added $Mn(OAc)_3$•$2H_2O$ (3.0 eq) and KI (0.5 eq). The reaction mixture was stirred at 80 °C for 22 h in the absence of light. The reaction was quenched with sat. $Na_2S_2O_3$ (aq) and extracted with EtOAc. The organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was further purified by FC ($PE_{40–60}$ / EtOAc).

4.5. General procedure 5: Krapcho decarboxylation

To a solution of bis-lactone (1 eq) in a mixture of DMSO (0.24 M) and H_2O (11.8 M) was added LiCl (3.5 eq). The reaction mixture was stirred at 160 °C for 1 h. The cooled mixture system was diluted with H_2O and extracted with Et_2O (unless otherwise noted). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude was used without further purification (unless otherwise noted).

4.6. General procedure 6: lactone α-methylenation

According to the procedure reported by Parker and Johnson,[41] to a solution of the substrate in anhydrous DMF was added $MeOMgOCO_2Me$ (Stile's reagent 2.0 M in DMF). The reaction mixture was stirred at 120 °C for 5 h. The cooled reaction mixture (0 °C) was then quenched with 6 M HCl followed by extraction with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the corresponding crude carboxylic acid.

To the crude carboxylic acid prepared above was added a measured amount of a stock solution composed of AcOH, NaOAc (0.105 g), formalin (2.9 mL) and Et_2NH (1.0 mL). The reaction mixture was stirred vigorously at RT until carbon dioxide evolution ceased. The solution was then heated to 100 °C for 10 min, cooled and diluted with H_2O. The mixture was extracted with EtOAc and the combined organic layers were washed with sat. $NaHCO_3$ (aq), brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude mixture was purified by FC.

4.7. General procedure 7: alkylation of alkyl malonates

According to the procedure of Logan *et al.*,[19] NaH (60 wt% in mineral oil, 3.0 eq) was suspended in anhydrous DMF (0.2 M) and cooled to 0 °C. Dialkyl malonate (3.0 eq) was added dropwise and the mixture was stirred for 20 min. A solution of alkenyl mesylate (1 eq) in anhydrous THF (0.2 M) was added dropwise, followed by KI (1 eq). The resultant mixture was stirred at 80 °C overnight. To the cool mixture was added sat. NH_4Cl (aq). The aqueous phase was extracted with EtOAc and the combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude was purified by FC ($PE_{40–60}$ / EtOAc).

4.8. Avenaciolide family of natural products: characterization

*4.8.1. (*E*)-Dodec-3-enoic acid* ***12***

Using general procedure 1 with malonic acid (2.2 g, 21.1 mmol) and decanal (3.6 mL, 19.2 mmol) in NMM (2.3 mL) gave **12** as a colourless gel (3.5 g, 17.7 mmol, 91%). R_f ($PE_{40–60}$ / Et_2O, 4 :1) = 0.6; δ_H (400 MHz, $CDCl_3$) 0.88 (t, 3 H, J = 7.0 Hz, CH_3CH_2), 1.23-1.38 (m, 12 H, 6 × CH_2), 2.03 (q, 2 H, J = 7.4 Hz, CH_2CH_2CHCH), 3.07 (dd, 2 H, J = 6.6, 0.9 Hz, $CHCHCH_2C$=O), 5.50 (dtt, 1 H, J = 15.3, 6.8, 1.2 Hz, $CHCHCH_2C$=O), 5.59 (dt, 1 H, J = 15.3, 6.5 Hz, $CHCHCH_2C$=O); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 22.8 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 32.0 (CH_2), 32.6 (CH_2), 37.9 (CH_2), 120.7 (CH), 135.8 (CH), 178.5 (C=O); *m/z* LRMS (ESI^-): 197.2 ([M-H]$^-$, 100%). Data in accordance to that reported in the literature.[32]

*4.8.2. (*E*)-Tetradec-3-enoic acid* ***13***

Using general procedure 1 with malonic acid (4.1 g, 39.6 mmol) and dodecanal (8.0 mL, 36.0 mmol) in NMM (4.4 mL)

gave **13** as a colourless gel (7.5 g, 33.1 mmol, 92%). R_f ($PE_{40–60}$ / Et_2O, 5:1) = 0.2; δ_H (500 MHz, $CDCl_3$) 0.88 (t, 3 H, *J* = 7.1 Hz, C*H*$_3$CH$_2$CH$_2$), 1.26-1.38 (m, 16 H, 8 × C*H*$_2$), 2.03 (q, 2 H, *J* = 6.8 Hz, CH$_2$C*H*$_2$CHCH), 3.07 (dd, 2 H, *J* = 6.8, 1.3 Hz, CHCHC*H*$_2$C=O), 5.50 (dtt, 1 H, *J* = 15.3, 6.8, 1.3 Hz, CHC*H*CH$_2$C=O), 5.59 (dtt, 1 H, *J* = 15.3, 6.6, 1.3 Hz, C*H*CHCH$_2$C=O); δ_C (125 MHz, $CDCl_3$) 14.3 (CH_3), 22.8 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 32.1 (CH_2), 32.6 (CH_2), 37.8 (CH_2), 120.7 (CH), 135.8 (CH), 177.6 (C=O); ν_{max} / cm^{-1} 2922s (O-H), 2853m (C-H), 1710s (C=O); *m/z* LRMS (ESI^-): 225.2 ([M-H]$^-$, 100%); HRMS (ESI^-) found 225.1857; $C_{14}H_{25}O_2$ [M-H]$^-$ requires 225.1860.

*4.8.3. Di-tert-butyl (*E*)-2-(hex-3-enoyloxy)malonate* **14**

Using general procedure 2 with di-*t*-butyl diazomalonate (3.8 g, 15.5 mmol), *trans*-hexenoic acid (1.6 mL, 13.9 mmol) and $Rh_2(OAc)_4$ (37 mg, 0.08 mmol) in benzene (55 mL). The residue was purified by FC ($PE_{40–60}$ / Et_2O, gradient from 15:1 to 7:1), giving the title compound **14** as a colorless oil (3.9 g, 78%). R_f ($PE_{40–60}$ / Et_2O, 7:1) = 0.6; δ_H (400 MHz, $CDCl_3$) 0.98 (t, 3 H, *J* = 7.5 Hz, C*H*$_3$CH$_2$CH), 1.49 (s, 18 H, 2 × OCC*H*$_3$), 2.05 (qn, 2 H, *J* = 7.5 Hz, CH$_3$C*H*$_2$CH), 3.20 (dd, 2 H, *J* = 6.7, 1.2 Hz, CHCHC*H*$_2$C=O), 5.32 (s, 1 H, OC*H*), 5.53 (dtt, 1 H, *J* = 15.3, 6.7, 1.5 Hz, CHC*H*CH$_2$C=O), 5.65 (dtt, 1 H, *J* = 15.3, 6.2, 1.2 Hz, C*H*CHCH$_2$C=O); δ_C (100 MHz, $CDCl_3$) 13.4 (CH_3), 25.5 (CH_2), 27.8 (CH_3), 37.3 (CH_2), 72.9 (CH), 83.4 (C), 119.6 (CH), 136.9 (CH), 163.6 (C=O), 170.9 (C=O); ν_{max} / cm^{-1} 2979w (C-H), 1746s (C=O), 1143s (C-O-C); *m/z* LRMS (ESI^+): 351.2 ([M+Na]$^+$, 100%); HRMS (ESI^+) found 329.1960; $C_{17}H_{29}O_6$ [M+H]$^+$ requires 329.1959.

*4.8.4. Di-*tert*-butyl (*E*)-2-(dodec-3-enoyloxy)malonate* ***15***

Using general procedure 2 with di-*t*-butyl diazomalonate (4.4 g, 17.9 mmol), **12** (3.2 g, 16.1 mmol) and $Rh_2(OAc)_4$ (43 mg, 0.09 mmol) in benzene (58 mL) gave crude material that was purified by FC ($PE_{40–60}$ / Et_2O, gradient from 20:1 to 8:1), to give the title compound **15** as a colorless oil (6.0 g, 14.5 mmol, 81%). R_f ($PE_{40–60}$ / Et_2O, 10:1) = 0.4; δ_H (500 MHz, $CDCl_3$) 0.87 (t, 3 H, *J* = 7.1 Hz, C*H*$_3$CH$_2$CH$_2$), 1.25-1.36 (m, 12 H, 6 × C*H*$_2$), 1.49 (s, 18 H, 2 × OCC*H*$_3$), 2.02 (q, 2 H, *J* = 7.1 Hz, CH$_2$C*H*$_2$CHCH), 3.19 (dd, 2 H, *J* = 6.5, 1.2 Hz, CHCHC*H*$_2$C=O), 5.32 (s, 1 H, OC*H*), 5.53 (dtt, 1 H, *J* = 15.4, 6.7, 1.2 Hz, CHC*H*CH$_2$C=O), 5.60 (dt, 1 H, *J* = 15.4, 6.6 Hz, C*H*CHCH$_2$C=O); δ_C (125 MHz, $CDCl_3$) 14.3 (CH_3), 22.8 (CH_2), 27.9 (CH_3), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 32.0 (CH_2), 32.6 (CH_2), 37.5 (CH_2), 73.0 (CH), 83.6 (C), 120.6 (CH), 135.8 (CH), 163.7 (C=O), 171.0 (C=O); ν_{max} / cm^{-1} 2927m (C-H), 2856w (C-H), 1748s (C=O), 1144s (C-O-C); *m/z* LRMS (ESI^+): 435.3 ([M+Na]$^+$, 100%); HRMS (ESI^+) found 435.2712; $C_{23}H_{40}O_6Na$ [M+Na]$^+$ requires 435.2717.

*4.8.5. Di-*tert*-butyl (*E*)-2-(tetradec-3-enoyloxy)malonate* ***16***

Using general procedure 2 with di-*t*-butyl diazomalonate (5.1 g, 20.9 mmol), **13** (4.2 g, 18.7 mmol) and $Rh_2(OAc)_4$ (50.0 mg, 0.11 mmol) in benzene (67 mL) gave crude material that was purified by FC ($PE_{40–60}$ / Et_2O, gradient from 20:1 to 7:1), to give the title compound **16** as a yellowish oil (7.2 g, 16.4 mmol, 88%). R_f ($PE_{40–60}$ / Et_2O, 10:1) = 0.4; δ_H (500 MHz, $CDCl_3$) 0.88 (t, 3 H, *J* = 7.2 Hz, C*H*$_3$CH$_2$CH$_2$), 1.25-1.36 (m, 16 H, 8 × C*H*$_2$), 1.49 (s, 18 H, OCC*H*$_3$), 2.02 (q, 2 H, *J* = 7.4 Hz, C*H*$_2$CHCHCH$_2$C=O), 3.18 (dd, 2 H, *J* = 6.5, 0.9 Hz, CHCHC*H*$_2$C=O), 5.32 (s, 1 H, OC*H*), 5.52 (dtt, 1 H, *J* = 15.4, 6.8, 1.3 Hz, CHC*H*CH$_2$C=O), 5.60 (dtt, 1 H, *J* = 15.4, 6.6, 1.2 Hz, C*H*CHCH$_2$C=O); δ_C (125 MHz, $CDCl_3$) 14.3 (CH_3), 22.8 (CH_2), 28.0 (CH_3), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 32.1 (CH_2), 32.7 (CH_2), 37.5 (CH_2), 73.0 (CH), 83.6 (C), 120.6 (CH), 135.8 (CH), 163.7 (C=O), 171.0 (C=O); ν_{max} / cm^{-1} 2925m (C-H), 1747s (C=O), 1142s (C-O-C); *m/z* LRMS (ESI^+): 463.2 ([M+Na]$^+$; 100%) HRMS (ESI^+) found 463.3021; $C_{25}H_{44}O_6Na$ [M+Na]$^+$ requires 463.3030.

*4.8.6. Di-*tert*-butyl-2-(but-3-enoyloxy)malonate* ***21***

Using general procedure 2 with di-*t*-butyl diazomalonate (3.80 g, 15.7 mmol), 3-butenoic acid (1.27 mL, 14.9 mmol) and $Rh_2(OAc)_4$ in benzene (60 mL) gave crude material that was purified by FC (PE_{40-60} °C / EtOAc, gradient from 12:1 to 6:1), to give **21** as a colorless oil (3.66 g, 12.2 mmol, 82%). R_f = 0.9 (PE_{40-60} / EtOAc, 10:1); δ_H (400 MHz, $CDCl_3$): 1.49 (s, 18 H, OCC*H*$_3$), 3.25 (dt, 2 H, *J* = 6.9, 1.4 Hz, CHCHC*H*$_2$C=O), 5.20 (ddd, 1 H, *J* = 10.3, 2.8, 1.4 Hz, C*H*$_{cis}$H$_{trans}$CHCH$_2$C=O), 5.21 (ddd, 1 H, *J* = 17.2, 3.0, 1.7 Hz, CH$_{cis}$*H*$_{trans}$CHCH$_2$C=O), 5.32 (s, 1 H, OC*H*), 5.94 (tdd, 1 H, *J* = 17.1, 10.3, 6.9 Hz, CH$_{cis}$H$_{trans}$C*H*CH$_2$C=O); δ_C (100 MHz, $CDCl_3$): 28.0 (CH_3), 38.5 (CH_2), 73.1 (CH), 83.6 (C), 119.3 (CH_2), 129.5 (CH), 163.6 (C=O), 170.3 (C=O); ν_{max} / cm^{-1} 2981w (C-H), 1744s (C=O), 1369m, 1250m, 1141s; *m/z* LRMS (ESI^+) 301.2 ([M+H]$^+$, 100%); HRMS (ESI^+) found 323.1462; $C_{15}H_{24}O_6Na$ [M+Na]$^+$ requires 323.1465.

*4.8.7. Di-*tert*-butyl 5-oxo-3-(prop-1-en-1-yl)dihydrofuran-2,2(3*H*)-dicarboxylate* ***18***

To a solution of **14** (3.9 g, 11.8 mmol), in MeCN (79 mL, previously sparged with Ar for 15 min) were added $Mn(OAc)_3$•$2H_2O$ (6.3 g, 23.6 mmol) and $Cu(OTf)_2$ (4.3 g, 11.8 mmol). The reaction mixture was stirred at 40 °C overnight then quenched with water and extracted with EtOAc. The organic layers were washed with sat. NH_4Cl (aq), brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by FC ($PE_{40–60}$ / Et_2O, gradient from 7:1 to 0:1) to give **18** as a white solid (1.6 g, 4.8 mmol, 40% isolated as an inseparable 3.8:1 mixture *E:Z* diastereomers). *Analysis is on the mixture of* E:Z *diastereomers*, R_f ($PE_{40–60}$ / Et_2O, 7:1) = 0.4; m.p. = 63-78 °C; δ_H (500 MHz, $CDCl_3$) (*E*)-**18**: 1.46 (s, 9 H, OCC*H*$_3$), 1.50 (s, 9 H, OCC*H*$_3$), 1.70 (ddd, 3 H, *J* = 6.5, 1.5, 1.0 Hz, CHCHC*H*$_3$), 2.65 (dd, 1 H, *J* = 17.4, 10.2 Hz, CH*H*CH), 2.69 (dd, 1 H, *J* = 17.4, 8.7 Hz, C*H*HCH), 3.64 (ddt, 1 H, *J* = 17.3, 8.7, 0.9 Hz, CHHC*H*), 5.42 (dddd, 1 H, *J* = 15.3, 7.2, 3.2, 1.5 Hz, CHC*H*CHCH$_3$), 5.66 (dqd, 1 H, *J* = 15.3, 6.5, 1.2 Hz, CHCHC*H*CH$_3$); (*Z*)-**18**: 1.48 (s, 9 H, OCC*H*$_3$), 1.49 (s, 9 H, OCC*H*$_3$), 1.75 (dd, 3 H, *J* = 6.9, 1.8 Hz, CHCHC*H*$_3$), 2.43 (dd, 1 H, *J* = 17.6, 7.8 Hz, C*H*HCH), 2.81 (dd, 1 H, *J* = 17.6, 8.8 Hz, CH*H*CH), 4.04 (dtd, 1 H, *J* = 10.4, 7.9, 0.9 Hz, CHHC*H*), 5.22 (tq, 1 H, *J* = 10.7, 1.8 Hz, CHC*H*CHCH$_3$), 5.63-5.70 (m, 1 H, CHCHC*H*CH$_3$, *masked*); δ_C (125 MHz, $CDCl_3$) (*E*)-**18**: 18.1 (CH_3), 27.9 (CH_3), 28.1 (CH_3), 33.2 (CH_2), 43.7 (CH), 83.8 (C), 84.3 (C), 87.7 (C), 125.7 (CH), 130.1 (CH), 165.0 (C=O), 165.1 (C=O), 174.2 (C=O); (*Z*)-**18**: 13.4 (CH_3), 27.9 (CH_3), 28.0 (CH_3), 34.9 (CH_2), 38.4 (CH), 83.9 (C), 84.1 (C), 87.9 (C), 125.4 (CH), 129.6 (CH), 164.6 (C=O), 165.0 (C=O), 173.2 (C=O); ν_{max} / cm^{-1} 2979w (C-H), 1803s (C=O), 1738s (C=O), 1153s (C-O-C); *m/z* LRMS (ESI^+): 349.2 ([M+Na]$^+$, 60%), 675.3 ([2M+Na]$^+$, 100%); HRMS (ESI^+) found 349.1619; $C_{17}H_{26}O_6Na$ [M+Na]$^+$ requires 349.1622. Further elution of the column gave the lactones **17** (770 mg, 2.9 mmol 24%) for which characterization data is reported later (*vide infra*).

*4.8.8. Di-*tert*-butyl 3-(1-chloropropyl)-5-oxodihydrofuran-2,2(3*H*)-dicarboxylate* ***20***

To a solution of **14** (1.0 g, 3.0 mmol), in MeCN (20 mL, previously sparged with Ar for 15 min) were added $Mn(OAc)_3$•$2H_2O$ (1.6 g, 6.1 mmol), $Cu(OTf)_2$ (1.1 g, 3.0 mmol)

and LiCl (155 mg, 3.6 mmol). The raction mixture was stirred at 40 °C for 22 h and then allowed to cool. The reaction was quenched with water and extracted with EtOAc. The organic layers were then washed with sat. NH_4Cl (aq) and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was further purified by FC ($PE_{40–60}$ / EtOAc, gradient from 10:1 to 0:1), to give the chloro-lactone **20** as a colorless oil (0.89 g, 2.4 mmol, 80% as an inseparable 3.3:1 mixture of unassigned diastereomers). *Analysis is on the mixture of diastereomers*, R_f ($PE_{40–60}$ / EtOAc, 4:1) = 0.7; δ_H (500 MHz, $CDCl_3$): **20-maj**: 1.08 (t, 3 H, *J* = 7.3 Hz, CHHCH_3), 1.50 (s, 9 H, OCCH_3), 1.54 (s, 9 H, OCCH_3), 1.69-1.79 (m, 1 H, C*H*HCH$_3$), 1.86 (dqd, 1 H, *J* = 14.5, 7.3, 4.4 Hz, CH*H*CH$_3$), 2.72 (dd, 1 H, *J* = 17.7, 9.0 Hz, O=CC*H*HCHCHCl), 2.85 (dd, 1 H, *J* = 17.7, 9.2 Hz, O=CCH*H*CHCHCl), 3.40 (td, 1 H, *J* = 9.1, 3.7 Hz, O=CCHHC*H*CHCl), 4.20 (dt, 1 H, *J* = 9.3, 4.1 Hz, CHC*H*Cl); **20-min**: 1.05 (t, 3 H, *J* = 7.2 Hz, CHHCH_3), 1.50 (s, 9 H, OCCH_3), 1.54 (s, 9 H, OCCH_3), 1.69-1.79 (2 H, C*HH*CH$_3$, *masked*), 2.68 (dd, 1 H, *J* = 17.8, 6.3 Hz, O=CC*H*HCHCHCl), 2.82 (dd, 1 H, *J* = 17.8, 8.9 Hz, O=CCH*H*CHCHCl), 3.57 (ddd, 1 H, *J* = 11.8, 6.2, 5.6 Hz, O=CCHHC*H*CHCl), 4.08 (ddd, 1 H, *J* = 10.8, 5.4, 2.2 Hz, CHC*H*Cl); δ_C (125 MHz, $CDCl_3$) **20-maj**: 11.5 (CH_3), 27.9 (CH_3), 28.0 (CH_3), 30.5 (CH_2), 31.3 (CH_2), 46.6 (CH), 62.6 (CH), 84.6 (C), 85.2 (C), 86.6 (C), 164.7 (C=O), 165.3 (C=O), 173.4 (C=O); **20-min**: 11.4 (CH_3), 27.2 (CH_2), 27.8 (CH_3), 28.0 (CH_3), 30.9 (CH_2), 47.5 (CH), 62.5 (CH), 84.7 (C), 85.1 (C), 86.9 (C), 164.4 (C=O), 164.7 (C=O), 173.3 (C=O); ν_{max} / cm^{-1} 2978w (C-H), 1805m (C=O), 1738s (C=O), 1151s (C-O-C); *m/z* LRMS (ESI^+): 385.1 ($[M+Na]^+$, 100%), 387.2 ($[M+Na]^+$, 30%); HRMS (ESI^+) found 385.1390 (100%), 387.1360 (30%); $C_{17}H_{27}{}^{35}ClO_6Na$ $[M+Na]^+$ requires 385.1388 and $C_{17}H_{27}{}^{37}ClO_6Na$ $[M+Na]^+$ requires 387.1359.

4.8.9. Di-tert-*butyl 3-(1-iodopropyl)-5-oxodihydrofuran-2,2(3*H*)-dicarboxylate **26** and* tert-*butyl (3a*R**,6a*R**)-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate **17***

Using general procedure 3 with **14** (500 mg, 1.5 mmol), $Mn(OAc)_3$•$2H_2O$ (818 mg, 3.1 mmol), $Cu(OTf)_2$ (550 mg, 1.5 mmol) and KI (379 mg, 2.3 mmol) in MeCN (10 mL) gave crude material that was purified by FC ($PE_{40–60}$ / EtOAc, gradient from 4:1 to 1:1), to give the iodo-lactone **26** as a yellow oil (146 mg, 0.32 mmol, 21%, as an inseparable 3.5:1 mixture of unassigned diastereomers). *Analysis is on the mixture of diastereomers*, R_f ($PE_{40–60}$ / EtOAc, 5:1) = 0.7; δ_H (400 MHz, $CDCl_3$) **26-maj**: 1.05 (t, 3 H, *J* = 7.2 Hz, CHHCH_3), 1.49 (s, 9 H, OCH_3), 1.54 (s, 9 H, OCH_3), 1.79-1.87 (m, 2 H, C*HH*CH$_3$), 2.66 (dd, 1 H, *J* = 17.7, 9.4 Hz, O=CC*H*HCH), 2.93 (dd, 1 H, *J* = 17.7, 8.7 Hz, O=CCH*H*CH), 3.32 (td, 1 H, *J* = 8.9, 7.4 Hz, O=CCHHC*H*), 4.13 (ddd, 1 H, *J* = 8.3, 7.4, 5.2 Hz, CHC*H*I); **26-min**: 0.99 (t, 3 H, *J* = 7.0 Hz, CHHCH_3), 1.49 (s, 9 H, OCH_3), 1.53 (s, 9 H, OCCH_3), 1.47-1.49 (CHHCH_3, *masked*), 2.74 (dd, 1 H, *J* = 18.0, 3.9 Hz, O=CC*H*HCH), 2.97 (dd, 1 H, *J* = 18.0, 9.0 Hz, O=CCH*H*CH), 3.79 (dt, 1 H, *J* = 8.9, 3.8 Hz, O=CCHHC*H*), 4.40 (ddd, 1 H, *J* = 11.6, 3.4, 2.3 Hz, CHC*H*I); δ_C (100 MHz, $CDCl_3$) **26-maj**: 15.0 (CH_3), 27.7 (CH_3), 27.9 (CH_3), 32.9 (CH_2), 37.8 (CH_2 and CH), 47.3 (CH), 81.6 (C), 84.5 (C), 85.1 (C), 164.9 (C=O), 166.2 (C=O), 172.2 (C=O); ν_{max} / cm^{-1} 1798m (C=O, lactone), 1736s (C=O, ester), 1147s (C-O-C); *m/z* LRMS (ESI^+): 477.0 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 477.0741; $C_{17}H_{27}IO_6Na$ $[M+Na]^+$ requires 477.0745. Further elution of the column gave the lactone **17** (53%) for which characterization is reported later.

4.8.10. Di-tert-*butyl 3-(iodomethyl)-5-oxodihydrofuran-2,2(3*H*)-dicarboxylate **29***

Using general procedure 3 with **21** (100 mg, 0.33 mmol) $Mn(OAc)_3$•$2H_2O$ (179 mg, 0.66mmol), $Cu(OTf)_2$ (121 mg, 0.33 mmol) and KI (66 mg, 0.40 mmol) in MeCN (2.2 mL) gave crude material that was purified by FC (PE_{40-60} / EtOAc, 85:15), to give **29** as a white solid (58 mg, 0.14 mmol, 41%). R_f = 0.8 (PE_{40-60} / EtOAc, 85 : 15); m.p. = 114-117 °C; δ_H (500 MHz, $CDCl_3$): 1.50 (s, 9 H, OCCH_3), 1.51 (s, 9 H, OCCH_3), 2.54 (dd, 1 H, *J* = 17.6, 11.0 Hz, O=CC*H*HCH), 2.88 (dd, 1 H, *J* = 11.9, 9.6 Hz, C*H*HI), 2.92 (dd, 1 H, *J* = 17.5, 8.5 Hz, O=CCH*H*CH), 3.37 (dtd, 1 H, *J* = 11.9, 8.5, 3.4 Hz, C*H*CHHI), 3.55 (dd, 1 H, *J* = 9.6, 3.5 Hz, CH*H*I); δ_C (125 MHz, $CDCl_3$): 0.7 (CH_2), 27.9 (CH_3), 28.1 (CH_3), 35.7 (CH_2), 44.6 (CH), 84.5 (C), 85.7 (C), 86.3 (C), 164.4 (C=O), 164.7 (C=O), 171.8 (C=O); ν_{max} / cm^{-1} 2979w (C-H), 1807s (C=O), 1736s (C=O) 1371m, 1313m, 1253m, 1150s; *m/z* LRMS (ESI^+) 449.0 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 449.0431; $C_{15}H_{23}IO_6Na$ $[M+Na]^+$ requires 449.0432. Further elution of the column gave **32** (12%). R_f = 0.2 (PE_{40-60} / EtOAc, 85:15); m.p. = 117-121 °C; δ_H (500 MHz, $CDCl_3$): 1.53 (s, 1 H, OCCH_3), 2.62 (dd, 1 H, *J* = 18.4, 5.9 Hz, O=CC*H*HCH), 3.04 (dd, 1 H, *J* = 18.4, 9.8, Hz, O=CCH*H*CH), 3.42 (dddd, 1 H, *J* = 9.6, 7.2, 5.9, 3.5 Hz, O=CCHHC*H*), 4.24 (dd, 1 H, *J* = 9.7, 3.5 Hz, CHC*H*HOC=O), 4.68 (dd, 1 H, *J* = 9.7, 7.2 Hz, CHCH*H*OC=O); δ_C (125 MHz, $CDCl_3$): 28.0 (CH_3), 33.5 (CH_2), 40.1 (CH), 70.9 (CH_2), 83.4 (C), 86.1 (C), 164.1 (C=O), 168.3 (C=O), 172.3 (C=O); ν_{max} / cm^{-1} 2927w (C-H), 1797s (C=O), 1783s (C=O), 1745s (C=O), 1107s; *m/z* HRMS (ESI^+) found 265.0683; $C_{11}H_{14}O_6Na$ $[M+Na]^+$ requires 265.0683.

4.8.11. tert-*Butyl (3a*R**,4*R**,6a**R*)-4-ethyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate **17-maj** and* tert-*butyl (3a*R**,4*S**,6a*R**)-4-ethyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate **17-min***

Using general procedure 4 with **14** (0.50 g, 1.52 mmol), $Mn(OAc)_3$•$2H_2O$ (1.22 g, 4.57 mmol) and KI (0.13 g, 0.76 mmol) in MeCN (10.0 mL) gave crude material that was purified by FC ($PE_{40–60}$ / EtOAc, gradient from 3:1 to 1:1), giving the title compounds **17** as a yellowish solid (0.32 g, 1.17 mmol, 77% yield, as an inseparable 2.8:1 mixture of C-4 diastereoisomers). *Analysis is on the mixture of diastereomers*, R_f ($PE_{40–60}$ / EtOAc, 1:1) = 0.7; m.p. = 110-114 °C; δ_H (500 MHz, $CDCl_3$) **17-maj**: 1.08 (t, 3 H, *J* = 7.4 Hz, CHHCH_3), 1.54 (s, 9 H, OCCH_3), 1.58-1.65 (m, 1 H, C*H*HCH$_3$), 1.80-1.94 (m, 1 H, CH*H*CH$_3$), 2.68 (dd, 1 H, *J* = 18.3, 9.1 Hz, C=OC*H*HCH), 2.75 (dd, 1 H, *J* = 18.3, 9.9 Hz, C=OCH*H*CH), 3.40 (m, 1 H, C=OCHHC*H*), 4.69 (dt, 1 H, *J* = 8.5, 6.0 Hz, CHC*H*OC=O); **17-min**: 1.07 (t, 3 H, *J* = 7.4 Hz, CHHCH_3), 1.53 (s, 9 H, OCCH_3), 1.58-1.65 (m, 1 H, C*H*HCH$_3$), 1.80-1.94 (m, 1 H, CH*H*CH$_3$), 2.57 (dd, 1 H, *J* = 18.3, 2.4 Hz, C=OC*H*HCH), 2.97 (dd, 1 H, *J* = 18.3, 9.4 Hz, C=OCH*H*CH), 3.06 (ddd, 1 H, *J* = 9.3, 5.9, 2.3 Hz, C=OCHHC*H*), 4.21 (dt, 1 H, *J* = 6.9, 5.9 Hz, CHC*H*OC=O); δ_C (125 MHz, $CDCl_3$) **17-maj**: 10.1 (CH_3), 27.9 (CH_2), 28.0 (CH_3), 28.1 (CH_2), 44.2 (CH), 80.7 (CH), 86.2 (C), 163.9 (C=O), 168.4 (C=O), 172.2 (C=O); **17-min**: 9.3 (CH_3), 24.5 (CH_2), 27.9 (CH_3), 33.3 (CH_2), 44.8 (CH), 85.9 (CH), 85.5 (C), 164.7 (C=O), 167.3 (C=O), 172.6 (C=O); ν_{max} / cm^{-1} 1787s (C=O), 1759m (C=O), 1108m (C-O-C); *m/z* LRMS (ESI^+): 563.2 ($[2M+Na]^+$, 100%); HRMS (ESI^+) found 563.2095; $C_{26}H_{36}O_{12}Na$ $[2M+Na]^+$ requires 563.2099.

4.8.12. tert-*Butyl (3a*R**,4*R**,6a**R*)-4-octyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate **30-maj** and* tert-*butyl (3a*R**,4*S,6aR*)-4-octyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate **30-min***

Using general procedure 4 with **15** (4.9 g, 11.97 mmol), $Mn(OAc)_3$•$2H_2O$ (9.6 g, 35.92 mmol), and KI (0.9 g, 5.99 mmol) in MeCN (80.0 mL) gave crude material that was purified by FC

($PE_{40–60}$ / EtOAc, gradient from 12:1 to 1:1) to give **30** as a yellowish solid (3.07 g, 8.66 mmol, 72% isolated as an inseparable 2.3:1 mixture of diastereomers). *Analysis is on the mixture of diastereomers*, R_f ($PE_{40–60}$ / EtOAc, 8:1) = 0.2; m.p. = 70-72 °C; δ_H (500 MHz, $CDCl_3$): **30-maj**: 0.87 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3), 1.25-1.43 (m, 12 H, 6 × CH_2), 1.51 (s, 9 H, $OCCH_3$), 1.71-1.78 (m, 1 H, O=COCHC*H*H), 1.81-1.89 (m, 1 H, O=COCHCH*H*), 2.58 (dd, 1 H, *J* = 18.3, 2.5 Hz, O=CC*H*HCH), 2.96 (dd, 1 H, *J* = 18.3, 9.5 Hz, O=CCH*H*CH), 3.05 (ddd, 1H, *J* = 9.3, 5.6, 2.4 Hz, O=CCHHC*H*), 4.27 (dt, 1 H, *J* = 7.6, 5.6 Hz, O=COC*H*CHH); **30-min**: 0.87 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3), 1.25-1.43 (m, 12 H, 6 × CH_2), 1.52 (s, 3 H, $OCCH_3$), 1.71-1.78 (m, 1 H, O=COCHC*H*H), 1.81-1.89 (m, 1 H, O=COCHCH*H*), 2.68 (dd, 1 H, *J* = 18.3, 9.1 Hz, O=CC*H*HCH), 2.74 (dd, 1 H, *J* = 18.3, 9.8 Hz, O=CCH*H*CH), 3.40 (ddd, 1 H, *J* = 9.7, 9.1, 5.8 Hz, O=CCHHC*H*), 4.74 (dt, 1 H, *J* = 8.6, 5.4 Hz, O=COC*H*CHH); δ_C (125 MHz, $CDCl_3$): **30-maj**: 14.2 (CH_3), 22.7 (CH_2), 25.0 (CH_2), 27.9 (CH_3), 29.2 (CH_2), 29.2 (CH_2), 29.4 (CH_2), 31.9 (CH_2), 33.3 (CH_2), 35.1 (CH_2), 45.1 (CH), 85.8 (CH), 84.8 (C), 85.0 (C), 164.7 (C=O), 167.5 (C=O), 172.8 (C=O); **30-min**: 14.2 (CH_3), 22.7 (CH_2), 25.7 (CH_2), 28.0 (CH_3), 28.0 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.1 (CH_2), 31.8 (CH_2), 44.3 (CH), 79.6 (CH), 85.4 (C), 86.0 (C), 163.9 (C=O), 168.5 (C=O), 172.4 (C=O); ν_{max} / cm^{-1} 2929m (C-H), 2957w (C-H), 1789s (C=O), 1759s (C=O); ***m/z*** LRMS (ESI^+): 377.2 ($[M+Na]^+$, 100%) ; HRMS (ESI^+) found 377.1931; $C_{19}H_{30}O_6Na$ $[M+Na]^+$ requires 377.1935.

4.8.13. tert-*Butyl (3a*R**,4*R**,6aR*)-4-decyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate **31-maj** and* tert-*butyl (3a*R**,4*S**,6a*R*)*-4-decyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate **31-min***

Using general procedure 4 with **16** (5.09 g, 11.56 mmol), $Mn(OAc)_3$•$2H_2O$ (9.30 g, 34.67 mmol) and KI (0.96 g, 5.78 mmol) in MeCN (77.0 mL) gave crude material that was purified by FC ($PE_{40–60}$ / EtOAc, gradient from 14:1 to 5:1) to give **31** as a yellowish solid (3.28 g, 8.58 mmol, 74% isolated as an inseparable 1.7:1 mixture of diastereomers). *Analysis is on the mixture of diastereomers*, R_f ($PE_{40–60}$ / EtOAc, 8:1) = 0.2; m.p. = 83-88 °C; δ_H (500 MHz, $CDCl_3$): **31-maj**: 0.88 (t, 3 H, *J* = 7.2 Hz, CH_2CH_3), 1.26-1.53 (m, 16 H, 8 × CH_2), 1.53 (s, 9 H, $OCCH_3$), 1.71-1.78 (m, 1 H, O=COCHC*H*H), 1.83-1.91 (m, 1 H, O=COCHCH*H*), 2.56 (dd, 1 H, *J* = 18.2, 2.3 Hz, O=CC*H*HCH), 2.96 (dd, 1 H, *J* = 18.2, 9.4 Hz, O=CCH*H*CH), 3.04 (ddd, 1 H, *J* = 9.3, 5.9, 2.3 Hz, O=CCHHC*H*), 4.24 (dt, 1 H, *J* = 7.8, 5.7 Hz, O=COC*H*CHH); **31-min**: 0.88 (t, 3 H, *J* = 7.2 Hz, CH_2CH_3), 1.26-1.53 (m, 16 H, 8 × CH_2), 1.54 (s, 9 H, $OCCH_3$), 1.71-1.78 (m, 1 H, O=COCHC*H*H), 1.83-1.91 (m, 1 H, O=COCHCH*H*), 2.68 (dd, 1 H, *J* = 18.3, 9.2 Hz, O=CC*H*HCH), 2.74 (dd, 1 H, *J* = 18.3, 9.8 Hz, O=CCH*H*CH), 3.38 (td, 1 H, *J* = 9.5, 5.7 Hz, O=CCHHC*H*), 4.75 (dt, 1 H, *J* = 8.8, 5.5 Hz, O=COC*H*CHH); δ_C (125 MHz, $CDCl_3$): **31-maj**: 14.3 (CH_3), 22.8 (CH_2), 25.1 (CH_2), 28.0 (CH_3), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 32.0 (CH_2), 33.3 (CH_2), 35.2 (CH_2), 45.3 (CH), 84.8 (CH), 84.9 (C), 85.9 (C), 164.7 (C=O), 167.3 (C=O), 172.6 (C=O); **31-min**: 14.3 (CH_3), 22.8 (CH_2), 25.7 (CH_2), 27.8 (CH_2), 28.0 (CH_3), 28.0 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 31.2 (CH_2), 32.0 (CH_2), 44.4 (CH), 79.5 (CH), 85.4 (C), 86.1 (C), 164.0 (C=O), 168.4 (C=O), 172.2 (C=O); ν_{max} / cm^{-1} 2926m (C-H), 2855w (C-H), 1789s (C=O), 1759m (C=O); *m/z* LRMS (ESI^+): 405.2 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 405.2246; $C_{21}H_{34}O_6Na$ $[M+Na]^+$ requires 405.2248.

*4.8.14. (3a*R**,4*R**,6a*R*)*-4-Ethyldihydrofuro[3,4-b]furan-2,6(3*H*,4*H*)-dione **33-maj** and (3a*R**,4*S**,6a*R*)*-4-ethyldihydrofuro[3,4-b]furan-2,6(3*H*,4*H*)-dione **33-min***

Using general procedure 5 with **17** (mixture of diastereomers, 3.95 g, 14.61 mmol), LiCl (2.17 g, 51.15 mmol) in DMSO (60.0 mL) and H_2O (1.25 mL); EtOAc was used as the extraction solvent and the residue was purified by FC ($PE_{40–60}$ / EtOAc, gradient from 3:1 to 1:1), to give **33** as a yellowish liquid (2.08 mg, 12.22 mmol, 80% isolated as an inseparable 2.03:1 mixture of diastereomers). *Analysis is on the mixture of diastereomers*, R_f ($PE_{40–60}$ / EtOAc, 2:1) = 0.2; δ_H (500 MHz, $CDCl_3$): **33-maj**: 1.05 (t, 3 H, *J* = 7.5 Hz, $CHHCH_3$), 1.79 (qdd, 1 H, *J* = 7.3, 5.9, 3.4 Hz, $CHHCH_3$), 1.81 (dqd, 1 H, *J* = 10.5, 7.5, 4.7 Hz, $CHHCH_3$), 2.56 (dd, 1 H, *J* = 18.2, 4.1 Hz, O=CC*H*HCH), 2.95 (dd, 1 H, *J* = 18.2, 9.5 Hz, O=CCH*H*CH), 3.05 (m, 1 H, O=CCHHC*H*), 4.30 (ddd, 1 H, *J* = 6.9, 5.9, 4.8 Hz, O=COC*H*CHHCH_3), 5.01 (d, 1 H, *J* = 7.8 Hz, O=COC*H*C=O); **33-min**: 1.07 (t, 3 H, *J* = 7.5 Hz, $CHHCH_3$), 1.63 (dqd, 1 H, *J* = 10.9, 7.4, 6.1 Hz, $CHHCH_3$), 1.89 (sept, 1 H, *J* = 7.4 Hz, $CHHCH_3$), 2.63 (dd, 1 H, *J* = 18.2, 9.5 Hz, O=CC*H*HCH), 2.64 (dd, 1 H, *J* = 18.2, 9.5 Hz, O=CCH*H*CH), 3.44-3.53 (m, 1 H, O=CCHHC*H*), 4.55 (dt, 1 H, *J* = 8.3, 5.9 Hz, O=COC*H*CHH), 5.16 (d, 1 H, *J* = 8.4 Hz, O=COC*H*C=O); δ_C (125 MHz, $CDCl_3$): **33-maj**: 9.3 (CH_3), 24.8 (CH_2), 33.0 (CH_2), 39.9 (CH), 77.1 (CH), 86.0 (CH), 169.9 (C=O), 173.6 (C=O); **33-min**: 9.9 (CH_3), 24.8 (CH_2), 26.9 (CH_2), 39.3 (CH), 77.1 (CH), 80.1 (CH), 170.5 (C=O), 173.7 (C=O); ν_{max} / cm^{-1} 2973w (C-H), 1777s (C=O), 1212m (C-O-C), 1150m (C-O-C), 1069m (C-O-C); *m/z* LRMS (ESI^+): 363.0 ($[2M+Na]^+$, 40%); HRMS (ESI^+) found 363.1050; $C_{16}H_{20}O_8Na$ $[2M+Na]^+$ requires 363.1050.

*4.8.15. (3a*R**,4*R**,6a*R*)*-4-Octyldihydrofuro[3,4-b]furan-2,6(3*H*,4*H*)-dione **34-maj** and (3a*R**,4*S**,6a*R*)*-4-octyldihydrofuro[3,4-b]furan-2,6(3*H*,4*H*)-dione **34-min***

Using general procedure 5 with **30** (mixture of diastereomers, 350 mg, 0.99 mmol), LiCl (147 mg, 3.46 mmol) in DMSO (6.6 mL) and H_2O (0.08 mL) gave **34** as brown oil (194 mg, 0.76 mmol, 77% isolated as a 2.23:1 inseparable mixture of diastereomers). *Analysis is on the mixture of diastereomers*, R_f ($PE_{40–60}$ / EtOAc, 5:1) = 0.16, 0.22; $\boldsymbol{\delta}_H$ (500 MHz, $CDCl_3$): **34-maj**: 0.88 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3), 1.25-1.84 (m, 14 H, 7 × CH_2), 2.55 (dd, 1 H, *J* = 18.2, 4.1 Hz, O=CC*H*HCH), 2.94 (dd, 1 H, *J* = 18.2, 9.4 Hz, O=CCH*H*CH), 3.04 (dddd, 1 H, *J* = 9.4, 7.9, 4.9, 4.1 Hz, O=CCHHC*H*), 4.34 (dt, 1 H, *J* = 7.6, 5.2 Hz, CHC*H*OC=O), 5.01 (d, 1 H, *J* = 7.9 Hz, O=COC*H*C=O); **34-min**: 0.88 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3), 1.25-1.84 (m, 14 H, 7 × CH_2), 2.63 (s apparent, 1 H, O=CC*H*HCH), 2.64 (s apparent, 1 H, O=CCH*H*CH), 3.46 (tdd, 1 H, *J* = 9.6, 8.4, 5.7 Hz, O=CCHHC*H*), 4.60 (dt, 1 H, *J* = 8.7, 5.7 Hz, CHC*H*OC=O), 5.16 (d, 1 H, *J* = 8.4 Hz, O=COC*H*C=O); $\boldsymbol{\delta}_C$ (125 MHz, $CDCl_3$): **34-maj**: 14.2 (CH_3), 22.8 (CH_2), 25.1 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 32.9 (CH_2), 35.6 (CH_2), 40.4 (CH), 77.1 (CH), 84.9 (CH), 169.9 (C=O), 173.6 (C=O); **34-min**: 14.2 (CH_3)), 22.8 (CH_2), 25.6 (CH_2), 27.0 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.6 (CH_2), 31.9 (CH_2), 39.6 (CH), 77.1 (CH), 78.8 (CH), 170.6 (C=O), 173.7 (C=O); ν_{max} / cm^{-1} 2925m (C-H), 2856w (C-H), 1781s (C=O), 1216w (C-O-C), 1150w (C-O-C); *m/z* LRMS (ESI^+): 531.4 ($[2M+Na]^+$, 100%); HRMS (ESI^+) found 277.1412; $C_{14}H_{22}O_4Na$ $[M+Na]^+$ requires 277.1410.

*4.8.16. (3a*R**,4*R* *6a*R*)*-4-Decyldihydrofuro[3,4-b]furan-2,6(3*H*,4*H*)-dione **35-maj** and (3a*R**,4*S**,6a*R*)*-4-decyldihydrofuro[3,4-b]furan-2,6(3*H*,4*H*)-dione **35-min***

Using general procedure 5 with **31** (mixture of diastereomers, 3.28 g, 8.58 mmol), LiCl (1.27 g, 30.01 mmol) in DMSO (36.0 mL) and H_2O (0.73 mL) gave **35** as a brown oil (2.33 g, 8.25

mmol, 96%, isolated as a 2.23:1 inseparable mixture of diastereomers). *Analysis is on the mixture of diastereomers*, R_f ($PE_{40–60}$ / EtOAc, 1:1) = 0.6, 0.7; δ_H (500 MHz, $CDCl_3$): **35-maj**: 0.88 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3), 1.26-1.85 (m, 18 H, 9 × CH_2), 2.55 (dd, 1 H, *J* = 18.2, 4.1 Hz, O=CC*H*HCH), 2.94 (dd, 1 H, *J* = 18.2, 9.4 Hz, O=CCH*H*CH), 3.03 (ddd, 1 H, *J* = 11.9, 7.8, 4.3 Hz, O=CCHHC*H*), 4.34 (dt, 1 H, *J* = 7.7, 5.2 Hz, CHC*H*OC=O), 5.00 (d, 1 H, *J* = 7.7 Hz, O=COC*H*C=O); **35-min**: 0.88 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3), 1.26-1.85 (m, 18 H, 9 × CH_2), 2.63 (d, 2 H, *J* = 9.5 Hz, O=CC*HH*CH), 3.46 (tdd, 1 H, *J* = 9.5, 8.4, 5.7 Hz, O=CCHHC*H*), 4.60 (dt, 1 H, *J* = 8.7, 5.7 Hz, CHC*H*OC=O), 5.15 (d, 1 H, *J* = 8.4 Hz, O=COC*H*C=O); δ_C (125 MHz, $CDCl_3$): **35-maj**: 14.3 (CH_3), 22.8 (CH_2), 25.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 32.0 (CH_2), 32.9 (CH_2), 35.6 (CH_2), 40.4 (CH), 77.1 (CH), 84.9 (CH), 173.6 (C=O), 173.7 (C=O); **35-min**: 14.3 (CH_3), 22.8 (CH_2), 25.6 (CH_2), 27.0 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 31.5 (CH_2), 32.0 (CH_2), 39.6 (CH), 77.1 (CH), 78.8 (CH), 169.9 (C=O), 170.6 (C=O); ν_{max} / cm^{-1} 2922m (C-H), 2854 (C-H), 1780s (C=O), 1214 (C-O-C), 1151 (C-O-C), 1074 (C-O-C); *m/z* HRMS (ESI^+) found 305.1723; $C_{16}H_{26}O_4Na$ $[M+Na]^+$ requires 305.1723.

4.8.17. Avenaciolide (major) ***1*** *and iso-avenaciolide (minor)* ***2***

Using general procedure 6 with **34** (mixture of diastereomers, 1.65 g, 6.49 mmol), DMF (15 mL), and $MeOMgOCO_2Me$ (2.0 M in DMF, 20.0 mL, 38.9 mmol) to give the corresponding crude acid. The crude acid was treated with the stock solution (7.20 mL). The crude product (7.3:1 mixture of diastereomers) was purified by FC ($PE_{40–60}$ / EtOAc, gradient from 3:1 to 1:2), to give **1** and **2** as white solids (avenaciolide **1**: 510 mg, 1.91 mmol, 34%) *iso*-avenaciolide **2**: 51 mg, 0.19 mmol, 26%).

avenaciolide **1**: R_f ($PE_{40–60}$ / EtOAc, 2:1) = 0.7; δ_H (500 MHz, $CDCl_3$): 0.88 (t, 3 H, *J* = 7.1 Hz, CH_2CH_3), 1.27-1.53 (m, 12 H, 6 × CH_2), 1.75-1.86 (m, 2 H, O=COCHC*HH*CHH), 3.53-3.57 (m, 1 H, O=CCC*H*CHOC=O), 4.42 (ddd, 1 H, *J* = 7.4, 5.9, 3.9 Hz, O=CCCHC*H*OC=O), 5.05 (d, 1 H, *J* = 8.5 Hz, O=COC*H*C=O), 5.87 (d, 1 H, *J* = 2.2 Hz, CC*H*H), 6.48 (d, 1 H, *J* = 2.2 Hz, CCH*H*); δ_C (125 MHz, $CDCl_3$): 14.2 (CH_3), 22.8 (CH_2), 24.9 (CH_2), 29.3 (2 × CH_2), 29.5 (CH_2), 31.9 (CH_2), 36.2 (CH_2), 44.3 (CH), 74.4 (CH), 85.2 (CH), 126.4 (CH_2), 134.7 (C), 167.6 (C=O), 169.8 (C=O); ν_{max} / cm^{-1} 2927m (C-H), 2856w (C-H), 1779s (C=O), 1294w, 1218w, 1105w, 1062w; *m/z* HRMS (ESI^+) found 267.1594; $C_{15}H_{23}O_4$ $[M+H]^+$ requires 267.1591. Data is in accordance to that reported in the literature.[15i]

iso-avenaciolide **2**: R_f ($PE_{40–60}$ / EtOAc, 2:1) = 0.3; δ_H (500 MHz, $CDCl_3$): 0.88 (t, 3 H, *J* = 7.1 Hz, CHHCH_3), 1.26-1.45 (m, 12 H, 6 × CH_2), 1.59-1.71 (m, 2 H, C*HH*CH_3), 3.99 (tt, 1 H, *J* = 8.5, 2.4 Hz, O=CCC*H*CHOC=O), 4.76 (ddd, 1 H, *J* = 10.0, 7.9, 3.4 Hz, O=CCCHC*H*OC=O), 5.11 (d, 1 H, *J* = 8.8 Hz, O=COC*H*C=O), 5.88 (d, 1 H, *J* = 2.3 Hz, CC*H*H), 6.60 (d, 1 H, *J* = 2.3 Hz, CCH*H*); δ_C (125 MHz, $CDCl_3$): 14.2 (CH_3), 22.8 (CH_2), 26.2 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 32.5 (CH_2), 41.9 (CH), 74.9 (CH), 80.6 (CH), 129.1 (CH_2), 130.9 (C), 167.9 (C=O), 170.1 (C=O); ν_{max} / cm^{-1} 2924w (C-H), 2854w (C-H), 1767 (C=O), 1218m (C-O-C), 1053m (C-O-C); *m/z* LRMS (ESI^+): 289.0 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 289.1414; $C_{15}H_{22}O_4Na$ $[M+Na]^+$ requires 289.1410. Data is in accordance to that reported in the literature.[15i]

4.8.18. epi-Ethisolide (major) ***4*** *and ethisolide (minor)* ***3***

Using general procedure 6 with **33** (mixture of diastereomers, 0.1 g, 0.59 mmol), DMF (2.9 mL), and $MeOMgOCO_2Me$ (2.0 M in DMF, 1.8 mL, 3.53 mmol) to give the corresponding crude acid. The crude acid was treated with the stock solution (0.65 mL). The crude product (4.3:1 mixture of diastereomers) was purified by FC ($PE_{40–60}$ / EtOAc, gradient from 2:1 to 1:2), to give **4** and **3** (*epi*-ethisolide **4**: 34 mg, 0.19 mmol, 34% and ethisolide **3**: 3.6 mg, 0.02 mmol, 18%).

epi-ethisolide **4**: R_f ($PE_{40–60}$ / EtOAc, 1:1) = 0.6; δ_H (500 MHz, $CDCl_3$): 1.08 (t, 3 H, *J* = 7.5 Hz, CHHCH_3), 1.85 (qd, 1 H, *J* = 7.0, 0.6 Hz, C*H*HCH_3), 1.87 (qd, 1 H, *J* = 7.0, 0.9 Hz, CH*H*CH_3), 3.58 (ddt, 1 H, *J* = 8.6, 3.9, 2.4 Hz, O=CCC*H*CH), 4.39 (td, 1 H, *J* = 6.5, 3.9 Hz, O=CCCHC*H*OC=O), 5.06 (dd, 1 H, *J* = 8.9, 0.3 Hz, O=COC*H*C=O), 5.88 (d, 1 H, *J* = 2.2 Hz, CC*H*H), 6.47 (d, 1 H, *J* = 2.2 Hz, CCH*H*); δ_C (125 MHz, $CDCl_3$): 9.2 (CH_3), 29.1 (CH_2), 43.8 (CH), 74.4 (CH), 86.4 (CH), 126.5 (CH_2), 134.7 (C), 167.6 (C=O), 169.9 (C=O); ν_{max} / cm^{-1} 2973w (C-H), 1771s (C=O), 1293m (C-O-C), 1216m (C-O-C), 1099m (C-O-C), 1059m (C-O-C); *m/z* LRMS (ESI^+): 183.0 ($[M+H]^+$, 100%), 205.0 ($[M+Na]^+$, 30%); HRMS (ESI^+) found 205.0473; $C_9H_{10}O_4Na$ $[M+Na]^+$ requires 205.0471. Data is in accordance to that reported in the literature.[15r]

ethisolide **3**: R_f ($PE_{40–60}$ / EtOAc, 1:1) = 0.3; δ_H (500 MHz, $CDCl_3$): 1.12 (t, 3 H, *J* = 7.3 Hz, CHHCH_3), 1.55-1.64 (m, 1 H, C*H*HCH_3), 1.72-1.80 (m, 1 H, CH*H*CH_3), 4.00 (tt, 1 H, *J* = 8.3, 2.5 Hz, O=CCC*H*CHOC=O), 4.68 (ddd, 1 H, *J* = 10.1, 7.9, 3.8 Hz, O=CCCHC*H*OC=O), 5.11 (d, 1 H, *J* = 8.8 Hz, O=COC*H*C=O), 5.88 (d, 1 H, *J* = 2.3 Hz, CC*H*H), 6.60 (d, 1 H, *J* = 2.3 Hz, CCH*H*); δ_C (125 MHz, $CDCl_3$): 10.8 (CH_3), 25.9 (CH_2), 41.8 (CH), 74.9 (CH), 81.9 (CH), 129.0 (CH_2), 130.9 (C), 167.9 (C=O), 170.0 (C=O); ν_{max} / cm^{-1} 2973w (C-H), 1772s (C=O), 1208m (C-O-C); *m/z* HRMS (ESI^+) found 205.04738; $C_9H_{10}O_4Na$ $[M+Na]^+$ requires 205.04713. Data is in accordance to that reported in the literature.[15i]

4.8.19. Discosiolide (major) ***5*** *and iso-discosiolide (minor)* ***6***

Using general procedure 6 with **35** (mixture of diastereomers, 1.62 g, 5.74 mmol), DMF (15 mL), and $MeOMgOCO_2Me$ (2.0 M in DMF, 17.0 mL, 34.4 mmol) to give the corresponding crude acid. The crude acid was treated with the stock solution (6.40 mL). The crude product (9:1 mixture of diastereomers) was purified by FC ($PE_{40–60}$ / EtOAc, gradient from 3:1 to 1:1), to give **5** and **6** as white solids (discosiolide **5**: 420 mg, 1.43 mmol, 28% and *iso*-discosiolide **6**: 17 mg, 0.06 mmol, 10%).

discosiolide **5**: R_f ($PE_{40–60}$ / EtOAc, 2:1) = 0.8; δ_H (500 MHz, $CDCl_3$): 0.88 (t, 3 H, *J* = 7.2 Hz, CHHCH_3), 1.27-1.50 (m, 16 H, 8 × CH_2), 1.75-1.86 (m, 2 H, C*HH*CH_3), 3.55 (ddt, 1 H, *J* = 8.5, 4.3, 2.3 Hz, O=CCC*H*CHOC=O), 4.43 (ddd, 1 H, *J* = 7.3, 5.9, 3.9 Hz, O=CCCHC*H*OC=O), 5.05 (d, 1 H, *J* = 8.5 Hz, O=COC*H*C=O), 5.87 (d, 1 H, *J* = 2.2 Hz, CC*H*H), 6.48 (dd, 1 H, *J* = 2.2 Hz, CCH*H*); δ_C (125 MHz, $CDCl_3$): 14.3 (CH_3), 22.8 (CH_2), 24.9 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 32.0 (CH_2), 36.3 (CH_2), 44.4 (CH), 74.4 (CH), 85.2 (CH), 126.4 (CH_2), 134.7 (C), 167.6 (C=O), 169.8 (C=O); ν_{max} / cm^{-1} 2924m (C-H), 2854m, 1780s (C=O); *m/z* HRMS (ESI^+) found 295.1910; $C_{17}H_{27}O_4$ $[M+H]^+$ requires 295.1904. Data is in accordance to that reported in the literature.[11]

iso-discosiolide **6** R_f ($PE_{40–60}$ / EtOAc, 2:1) = 0.3; δ_H (500 MHz, $CDCl_3$): 0.88 (t, 3 H, *J* = 7.1 Hz, CHHCH_3), 1.26-1.69 (m, 18 H, 9 × CH_2), 3.98 (tt, 1 H, *J* = 8.5, 2.4 Hz, O=CCC*H*CHOC=O), 4.75 (ddd, 1 H, *J* = 10.2, 8.0, 3.5 Hz, O=CCCHC*H*OC=O), 5.10 (d, 1 H, *J* = 8.7 Hz, O=COC*H*C=O), 5.88 (d, 1 H, *J* = 2.3 Hz, CC*H*H), 6.61 (d, 1 H, *J* = 2.3 Hz, CCH*H*); δ_C (125 MHz, $CDCl_3$): 14.3 (CH_3), 22.8 (CH_2), 26.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 32.0 (CH_2), 32.6 (CH_2), 41.9 (CH), 74.8 (CH), 80.1 (CH),

129.1 (CH_2), 130.9 (C), 167.9 (C=O), 170.0 (C=O); ν_{max} / cm^{-1} (C=C), 1252m, 1139s (C-O-C); *m/z* HRMS (ESI^+) found 2924m, 2853w (C-H), 1767s (C=O), 1218w; *m/z* HRMS (ESI^+) found 295.1904; $C_{17}H_{27}O_4$ $[M+H]^+$ requires 295.1904.

*4.8.20. Di-*tert*-butyl 2-(pent-4-en-1-yl)malonate **36***

Using general procedure 7 with NaH (1.2 g, 28.9 mmol, 60 wt% in mineral oil), di-*tert*-butyl malonate (6.5 mL, 28.9 mmol) in anhydrous DMF (90 mL), and the corresponding alkenyl mesylate[33] (1.9 g, 11.6 mmol) and KI (1.9 g, 11.6 mmol) in anhydrous THF (58 mL) gave crude material that was purified by FC ($PE_{40–60}$ / EtOAc, 95:5), to give **6** as a colourless oil (2.36 g, 8.3 mmol, 72% yield). R_f = 0.8 ($PE_{40–60}$ / EtOAc, 95:5); δ_H (400 MHz, $CDCl_3$): 1.40-1.44 (m, 2 H, $CH_2CH_2CH_2$, *masked*), 1.45 (s, 18 H, $OCCH_3$), 1.81 (dt, 2 H, *J* = 8.2, 7.6 Hz, CH_2CH_2CH), 2.07 (ddt, 2 H, *J* = 14.2, 6.9, 1.3 Hz, $CHCHCH_2CH_2$), 3.12 (t, 1 H, *J* = 7.6 Hz, $CH_2CH_2CH_2CH$), 4.95 (ddt, 1 H, *J* = 10.2, 2.0, 1.2 Hz, $CHHCHCH_2$), 5.01 (dq, 1 H, *J* = 17.2, 1.6 Hz, $CHHCHCH_2$), 5.78 (ddt, 1 H, *J* = 17.2, 10.4, 6.8 Hz, $CHHCHCH_2$); δ_C (100 MHz, $CDCl_3$): 26.5 (CH_2), 27.9 (CH_3), 28.0 (CH_2), 33.4 (CH_2), 53.8 (CH), 81.2 (C), 114.8 (CH_2), 138.2 (CH), 168.9 (C=O); ν_{max} / cm^{-1} 2979w (C-H), 1727s (C=O), 1393m, 1138s (C-O-C); *m/z* LRMS (ESI^+): 307.2 ($[M+Na]^+$, 67%), 591.4 ($[2M+Na]^+$, 100%); HRMS (ESI^+) found 307.1874; $C_{16}H_{28}O_4Na$ $[M+Na]^+$ requires 307.1879.

4.8.21. tert*-Butyl (3a*S**,6a*S**)-3-oxotetrahydro-1H-cyclopenta[c]furan-3a(3*H*)-carboxylate **38***

Using general procedure 4 with **36** (100 mg, 0.35 mmol), $Mn(OAc)_3$•$2H_2O$ (282 mg, 1.1 mmol) and KI (29 mg, 0.18 mmol) in MeCN (2.4 mL) gave crude material that was purified by FC (PE_{40-60} / EtOAc, gradient from 14:1 to 12:1) to give **38** as a white solid (37 mg, 0.16 mmol, 46% yield). R_f = 0.4 (PE_{40-60} / EtOAc, 8:1); δ_H (400 MHz, $CDCl_3$): 1.46 (s, 9 H, $OCCH_3$), 1.57-1.66 (m, 2 H, $CHHCHHCHHCC=O$, $CHHCHHCHHCC=O$), 1.74-1.83 (m, 1 H, $CHHCHHCHHCC=O$), 1.99-2.09 (m, 1 H, $CHHCHHCHHCC=O$), 2.14-2.21 (m, 1 H, $CHHCHHCHHCC=O$), 2.29-2.37 (m, 1 H, $CHHCHHCHHCC=O$), 2.98-3.04 (m, 1 H, $CHCHHOC=O$), 4.07 (dd, 1 H, *J* = 9.2, 2.2 Hz, $CHCHHOC=O$), 4.52 (dd, 1 H, J = 9.2, 7.4 Hz, , $CHCHHOC=O$); δ_C (100 MHz, $CDCl_3$): 26.1 (CH_2), 27.9 (CH_3), 34.1 (CH_2), 34.2 (CH_2), 46.1 (CH), 62.7 (C), 73.2 (CH_2), 82.9 (C), 169.0 (C=O), 177.1 (C=O); ν_{max} / cm^{-1} 2975w (C-H), 2874w (C-H), 1769s (C=O), 1732s (C=O), 1369m, 1257m (C-O-C), 1139s (C-O-C); *m/z* LRMS (ESI^+): 227.0 ($[M+H]^+$, 100%); HRMS (ESI^+) found 227.1280; $C_{12}H_{19}O_4$ $[M+H]^+$ requires 227.1278.

*4.8.22. Di-*tert*-butyl (E)-2-(5-phenylpent-4-en-1-yl)malonate **37***

Using general procedure 7 with di-*tert*-butyl malonate (8.4 mL, 37.4 mmol) and NaH (1.5 g, 37.4 mmol, 60 wt% in mineral oil) in DMF (65 mL), and the corresponding phenyl alkenyl mesylate[19] (3.0 g, 12.5 mmol) and KI (2.1 g, 12.5 mmol) in THF (30 mL) gave crude material that was purified by FC ($PE_{40–60}$ / EtOAc, gradient from 50:1 to 40:1) to give **37** as a white solid (2.4 g, 6.7 mmol, 53% yield). R_f = 0.3 ($PE_{40–60}$ / EtOAc, 20:1); m.p. = 39-45 °C; δ_H (400 MHz, $CDCl_3$): 1.46 (s, 18 H, $OCCH_3$), 1.40-1.52 (m, 2 H, $CH_2CH_2CH_2$), 1.86 (dt, 2 H, *J* = 8.1, 7.8 Hz, CH_2CH_2CH), 2.24 (q, 2 H, *J* = 7.2 Hz, $CHCH_2CH_2$), 3.14 (t, 1 H, *J* = 7.6 Hz, CH_2CH_2CH), 6.19 (dt, 1 H, *J* = 15.8, 6.9 Hz, $PhCHCHCH_2$), 6.38 (d, 1 H, *J* = 15.8 Hz, $PhCHCHCH_2$), 7.17-7.20 (m, 1 H, C(Ar)*H*), 7.26-7.34 (m, 4 H, C(Ar)*H*); δ_C (400 MHz, $CDCl_3$): 27.1 (CH_2), 28.1 (CH_3), 28.3 (CH_2), 32.9 (CH_2), 53.9 (CH), 81.5 (C), 126.1 (2 x C(Ar)), 127.0 (C(Ar)), 128.6 (2 x C(Ar)), 130.3 (CH), 130.4 (CH), 137.8 (C(Ar)), 169.1 (C=O); ν_{max} / cm^{-1} 2978w (C-H), 2934w (C-H), 1725s (C=O), 1368m (C=C), 1252m, 1139s (C-O-C); *m/z* HRMS (ESI^+) found 361.2373 ; $C_{22}H_{33}O_4$ $[M+H]^+$ requires 361.2373.

4.8.23. tert*-Butyl (1*S**,3a*S**,6a*S**)-3-oxo-1-phenyltetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate **39-maj** and* tert*-butyl (1*R**,3a*S**,6a*S**)-3-oxo-1-phenyltetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate **39-min***

Using general procedure 4 with **37** (60 mg, 0.17 mmol), $Mn(OAc)_3$•$2H_2O$ (134 mg, 0.49 mmol) and KI (28 mg, 0.17 mmol) in MeCN (1.1 mL) gave crude material that was purified by FC ($PE_{40–60}$ / EtOAc, gradient from 20:1 to 10:1) to give **39** as a white solid (49 mg, 0.16 mmol, 88%, isolated as a 9:1 inseparable mixture of diastereomers). *Analysis is on the mixture of diastereomers but only data for the major diastereomer is reported*). R_f = 0.2 ($PE_{40–60}$ / EtOAc, 12:1); δ_H (500 MHz, $CDCl_3$): 1.38 (s, 9 H, $OCCH_3$), 1.70 (m, 1 H, $CHHCHHCHHCC=O$), 1.89-2.05 (m, 3 H, $CHHCHHCHHCC=O$, $CHHCHHCHHCC=O$ and $CHHCHHCHHCC=O$), 2.27 (ddd, 1 H, *J* = 12.8, 6.7, 2.3 Hz, $CHHCHHCHHCC=O$), 2.41 (ddd, 1 H, *J* = 13.4, 11.3, 6.7 Hz, $CHHCHHCHHCC=O$), 3.06-3.09 (m, 1 H, $CHCHOC=O$), 5.02 (d, 1 H, *J* = 4.6 Hz, $CHCHOC=O$); δ_C (500 MHz, $CDCl_3$): 25.7 (CH_2), 27.8 (CH_3), 34.0 (CH_2), 35.0 (CH_2), 54.8 (CH), 63.3 (C), 82.9 (C), 86.1 (CH, 125.5 (2 × CH), 128.5 (CH), 128.8 (2 ×CH), 140.4 (C), 169.5 (C=O), 176.6 (C=O); ν_{max} / cm^{-1} 2976w (C-H), 1773s (C=O), 1732s (C=O), 1455w (C=C), 1394m, 1256m, 1144s (C-O-C); *m/z* LRMS (ESI^+): 325.2 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 325.1410; $C_{18}H_{22}O_4Na$ $[M+Na]^+$ requires 325.1410.

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Supplementary Material

^{1}H and ^{13}C NMR of synthetic intermediates and natural products **1**-**5** and natural product analogue **6**.