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**PAPER**

# Total synthesis and structural elucidation of *ent*-micropyrone and (+)-ascosalipyrone†

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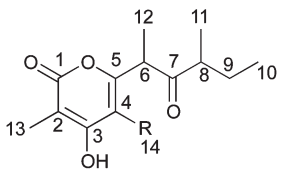
The total synthesis of 6-[(1*S*,3*S*)-1,3-dimethyl-2-oxopentyl]-4-hydroxy-3,5-dimethyl-2*H*-pyran-2-one (**22**), the enantiomer of the natural product micropyrone (**1**), was achieved in 9 linear steps (10% overall yield), from Evans auxiliary (*R*)-**12** with key coupling of the dianion of dione **17** and aldehyde **11**. Formation of the pyrone ring and subsequent oxidation at C7 was achieved without epimerization of the sensitive position α to both the pyrone ring and the carbonyl. The same sequence using the alternate dione **24** achieved the total synthesis of 6-[(1*S*,3*S*)-1,3-dimethyl-2-oxopentyl]-4-hydroxy-3-methyl-2*H*-pyran-2-one (**28**), the (+)-enantiomer of the natural product, ascosalipyrone (**2**). In both cases diastereomeric aldehydes **11** and **16** were taken through the synthetic sequence to give two possible diastereomers of the natural products. Comparison of the $^{1}$H and $^{13}$C NMR data for the synthetic isomers with that reported for the natural products determined their relative stereochemistry. Comparison of the optical rotation obtained for **22** established it to be the enantiomer of micropyrone.

## Introduction

The α-pyrone ring is a structural feature present in numerous polyketide natural products isolated from a wide variety of sources and is associated with many key biological processes including defense and intercellular communication.[1] Many biologically important compounds contain the α-pyrone moiety, including pheromones, coumarins and elasnin, and they display broad spectrum pharmaceutical properties including use in the treatment of HIV, Alzheimer's disease and cancer.[1] 4-Hydroxy-α-pyrones in particular have become one of the most important classes of anti-HIV agents.[2]

Micropyrone (**1**) (Fig. 1) was isolated from *Helichrysum italicum* ssp. *microphyllum* in 2007 by Appendino and coworkers.[3] The structure of micropyrone (**1**) was assigned on the basis of $^{1}$H and $^{13}$C NMR data to contain a 4-hydroxy-α-pyrone ring and is potentially related to a series of β-diketones isolated from the essential oil of *H. italicum*.[4,5] The absolute and relative configuration of the two stereocentres was not determined, but it appeared from a single set of $^{1}$H and $^{13}$C resonances to be a single stereoisomer. The isolation of this compound as a single isomer implies that the presence of the carbonyl β to the pyrone ring does not lead to rapid epimerization of the α-stereocentre under physiological conditions or during the isolation process. A structurally related compound, ascosalipyrone (**2**), had previously been isolated from the endophytic and obligate marine fungus *Ascochyta salicorniae* of the green alga *Ulva* sp. in 2000 by the group of König.[6] Ascosalipyrone (**2**) was subsequently tested for its inhibition of a variety of protein phosphatases, but showed no activity.[7] Ascosalipyrone (**2**) was reported[6] to have a structure which differed from micropyrone only in the absence of the methyl at C4 of the pyrone ring. The relative and absolute configuration of ascosalipyrone (**2**) was not determined and it appeared from some split signals in the $^{13}$C NMR that it was an unequal mixture of diastereomers.




R = Me, Micropyrone (**1**)
R = H, Ascosalipyrone (**2**)

**Fig. 1** Structures of micropyrone[3] and ascosalipyrone.[6]

There are four possible stereoisomers **3**–**6** (two pairs of enantiomers) each for micropyrone (**1**) and ascosalipyrone (**2**)

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†Electronic supplementary information (ESI) available: General experimental details, detailed experimental procedures and spectroscopic data for compounds **11**, **13**–**17**, **26**–**30**, and **33**–**46**, copies of $^{1}$H and $^{13}$C NMR spectra of compounds **11**, **14**, **16**, **18**, **20**, **22**, **23**, **25**–**29**, **37**, **39**, **41**, **43** & **44** and X-ray crystallographic data and cif files for compounds **22** & **23**. CCDC 870497 and 870498. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25501d

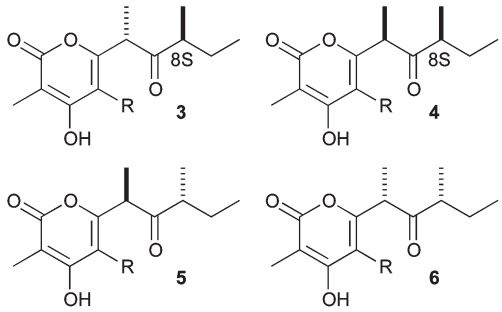
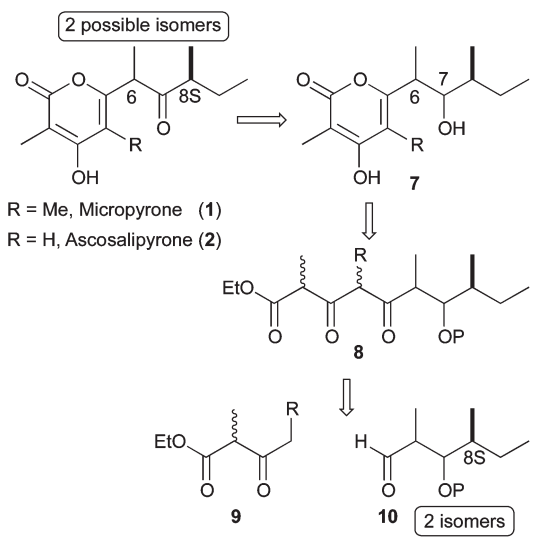



**Fig. 2** Possible isomers of micropyrone (R = Me) and ascosalipyrone (R = H).

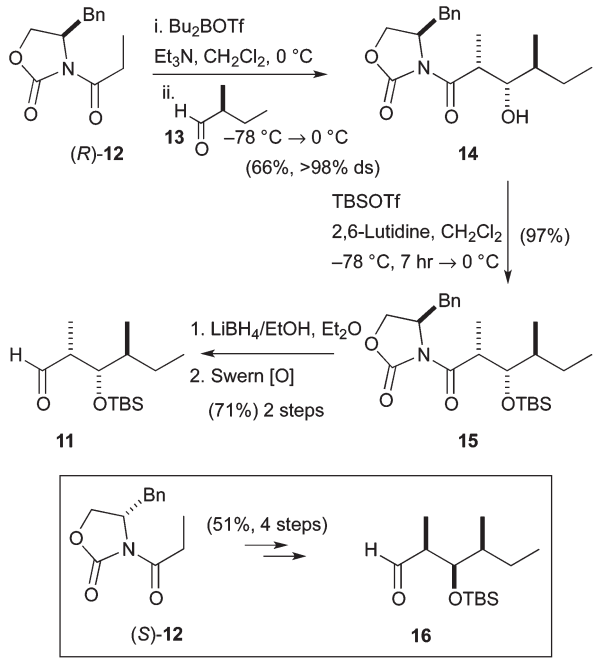
(Fig. 2). We proposed to use a common strategy to prepare the two isomers **3** and **4** (8*S* configuration in each case) of each natural product in order to establish their absolute and relative configurations.

## Results and discussion

The common synthetic strategy for the preparation of both micropyrone (**1**) and ascosalipyrone (**2**) is shown in Scheme 1. It was hoped that oxidation of the alcohol at C7 in compound **7** would give the β-ketone pyrones without epimerization of the C6 stereocentre in the final synthetic step. It was further proposed that cyclisation of the trione **8** and subsequent deprotection would give the pyrone ring containing **7**. Compound **8** was to be prepared by oxidation of the product from addition of the dianion of **9** to aldehyde **10**. Compound **9** (R = Me) will give micropyrone (**1**) and alternately use of **9** (R = H) will give ascosalipyrone (**2**). Use of two different isomers of **10** will allow specific preparation of the 6*R* and 6*S* stereoisomers of the two natural products. Stereocontrolled synthesis of appropriate isomers of **10** was to be achieved using an Evans auxiliary[8] based benzyl oxazolidinone protocol.




**Scheme 1** Retrosynthetic analysis of micropyrone (**1**) and ascosalipyrone (**2**).



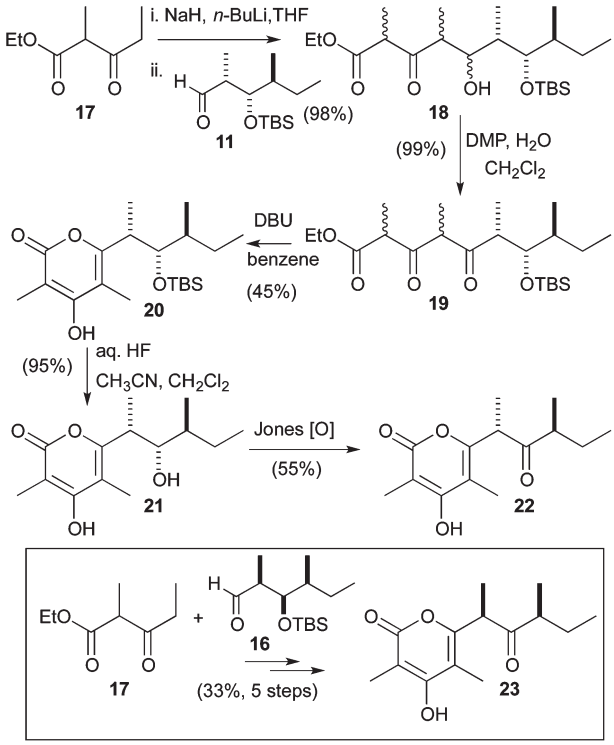

**Scheme 2** Synthesis of aldehydes **11** and **16**.

Synthesis of the *syn–anti* aldehyde **11** began with an asymmetric aldol reaction between the dibutylboron enolate of the Evans auxiliary[8–10] (*R*)-**12** and the α-chiral aldehyde **13** (obtained by Swern oxidation[11] of (*S*)-2-methylbutan-1-ol) as shown in Scheme 2. This double stereodifferentiating aldol reaction of Evans auxiliary[8–10] (*R*)-**12** is expected to be matched with the *anti*-Felkin preference[12] of aldehyde **13** and gave the product **14**[13] with no detectable minor isomer (66%, >98% ds). Silyl protection (TBSOTf, 2,6-lutidine)[14] yielded compound **15**[15] in good yield. Conversion to aldehyde **11** was achieved by reduction to the primary alcohol ($LiBH_4$), and subsequent Swern oxidation[11] (71% yield over 2 steps). Use of the enantiomer of the Evans auxiliary (*S*)-**12** and the α-chiral aldehyde **13** in the same four step sequence gave the isomeric *syn–syn* aldehyde **16** in 51% yield. In this sequence the stereoselectivity of the aldol between (*S*)-**12** and the α-chiral aldehyde **13** is equally high (>98% ds) indicating little effect from any facial preference of aldehyde **13**. When the two diastereomeric aldehydes **11** and **16** are taken through the subsequent sequence they will give the two possible C6 epimers of the natural products.

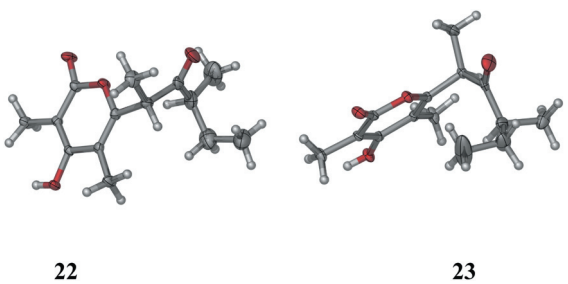
With the two required aldehydes **11** and **16** in hand we attempted the dianion addition using **17** prepared by the dimerisation of ethyl propionate (Scheme 3).[16] Dione **17** was first deprotonated with NaH followed by *n*-butyl lithium, then aldehyde **11** was added giving the product **18** as an inseparable mixture of isomers (98%). Oxidation of the product with Dess–Martin[17] periodinane gave the trione **19** as an isomeric mixture with a number of keto and enol forms apparent by NMR spectroscopy. The trione was cyclised using DBU in benzene at 60 °C to give pyrone **20** as a single stereoisomer. The *t*-butyldimethylsilyl protecting group was simply removed using aqueous HF/$CH_3CN$ to give alcohol **21**. Compound **21** proved to be very insoluble but could be purified simply by triturating with acetone. It was envisioned that a mild neutral oxidation would






**Scheme 3** Synthesis of two possible isomers (**22** and **23**) of micropyrone.

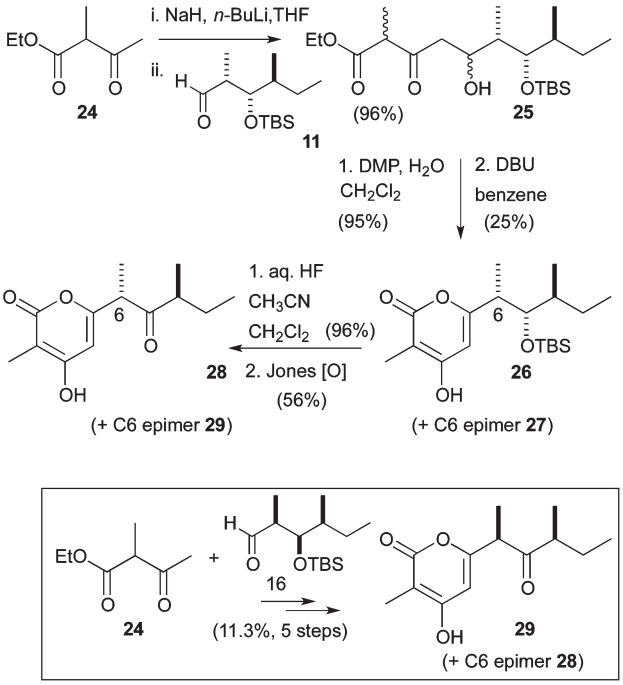


**22** **23**

**Fig. 3** X-ray crystal structures of the two possible isomers (**22** and **23**) of micropyrone.

be employed in the final step of the synthesis to avoid epimerization of the C6 stereocentre of β-keto pyrone **22**. But attempted oxidation of **21** using either Swern or Dess–Martin conditions were not successful, apparently as a result of the insolubility of **21**. Fortunately, oxidation using Jones reagent[18] was successful giving the desired product **22** as a single isomer without C6 epimerization.

Use of dione **17** and the diastereomeric aldehyde **16** in the same five step sequence gave the C6 epimeric β-ketone pyrone **23**. Notably both these products were crystalline solids and crystals suitable for X-ray analysis were grown. Single crystal structural analysis confirmed the assigned structures of the two isomers including the configuration at C6 (Fig. 3). Notably in both cases the conformation around the C5–C6 bond places the small C6–H eclipsing the C4–Me thus minimising the $A^{1,3}$ strain of this flanking methyl. This low energy conformation also suggests the configurational stability of the C6 stereocentre (between the pyrone ring and the carbonyl) may be explained by




**Scheme 4** Synthesis of two possible isomers (**28** and **29**) of ascosalipyrone.

the unfavorable $A^{1,3}$ strain that would be present in the planar enol tautomer.

The preparation of the two possible isomers of ascosalipyrone (**2**) is shown in Scheme 4. The same 5 step sequence as indicated in Scheme 3 was employed using the dianion of **24** with each aldehyde **11** and **16**. In this case addition of the dianion of dione **24** to aldehyde **11** uneventfully gave product **25**. However, after Dess–Martin oxidation (95%) and cyclisation using DBU, the product **26** was isolated as a ~3 : 1 mixture of the product **26** and the C6 epimer **27**. Thus it appeared that partial epimerization had occurred at C6 during cyclisation to form the pyrone ring. As separation was not possible, this mixture was taken through the last two steps of deprotection and oxidation. Again, insolubility meant that Jones oxidation proved to be the only viable oxidant and product **28** was isolated, contaminated with ~25% of its C6 epimer **29**. The same reaction sequence was also carried out using dione **24** and aldehyde **16** to give pyrone **29** as the major product (contaminated with ~25% of the C6 epimer **28**).

With the two possible diastereomers of each of the natural products micropyrone (**1**) and ascosalipyrone (**2**) in hand, $^{1}H$ and $^{13}C$ NMR spectral comparison and optical rotation comparison were then used to assign the relative and absolute configurations of the natural products. Fig. 4 shows the difference between the $^{13}C$ NMR data for micropyrone (**1**) and synthetic isomers **22** and **23**. The chemical shifts observed for carbons 6, 9 and 11 of *syn* isomer **23** are significantly different (≥1 ppm) from those reported for micropyrone (**1**) while all the $^{13}C$ chemical shifts of *anti* isomer **22** are ≤0.2 ppm different from those reported for the natural product. There is also a near perfect match between the $^{1}H$ NMR of *anti* isomer **22** and the natural product whereas significant differences are seen for the *syn* isomer **23**. On this basis the relative configuration of micropyrone (**1**) is assigned as

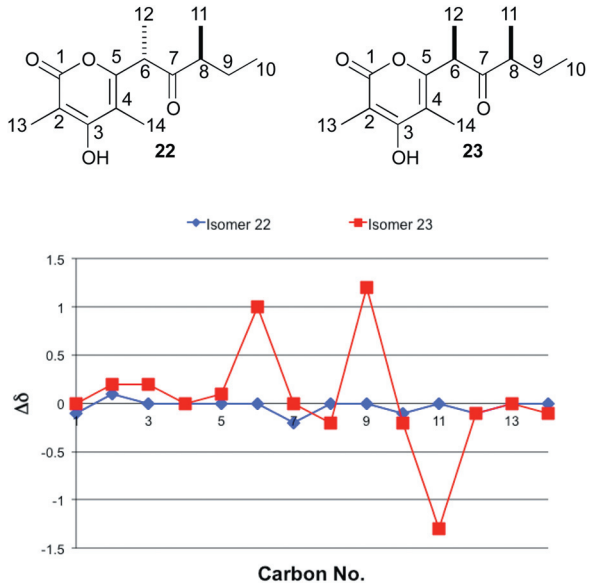



**Fig. 4** Difference in chemical shift ($\Delta\delta$) for micropyrone (**1**) and synthetic isomers **22** and **23**.

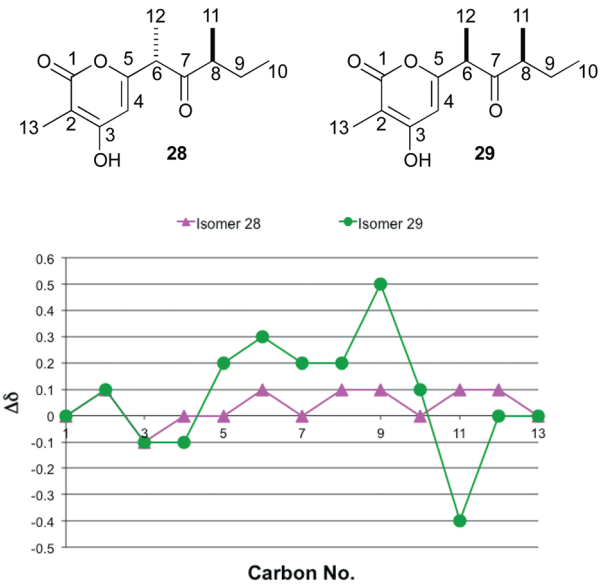



**Fig. 5** Difference in chemical shift ($\Delta\delta$) for ascosalipyrone (**2**) and synthetic isomers **28** and **29**.

*anti* isomer **22**. The observed rotation for *anti* isomer **22** was $[\alpha]_D^{20}$ = +28.8 (*c* 1.36, MeOH) which is of the opposite sign to that reported ($[\alpha]_D^{20}$ = −21 (*c* 1.0, MeOH)) for the natural product, showing that the natural product micropyrone (**1**) is the *enantiomer* of compound **22**.

Fig. 5 shows a comparison of the $^{13}C$ NMR data for ascosalipyrone (**2**) and synthetic isomers **28** and **29**. All the $^{13}C$ chemical shifts of isomer **28** are ≤0.1 ppm different from those reported for the natural product, while variation of >0.1 ppm is seen in carbons 5–9 and 11 of the $^{13}C$ chemical shifts of isomer **29**. In this case however there are no significant differences in the $^{1}H$ NMR chemical shifts for either isomer. On the basis of the differences in the $^{13}C$ chemical shifts, the relative configuration of ascosalipyrone (**4**) is assigned as *anti* isomer **28**. The observed rotation for diastereomer **28** (as a 3 : 1 mixture with its C6 epimer **(6*R*,8*S*)-4**) was $[\alpha]_D^{20}$ = +60.7 (*c* 1.57, MeOH), however no optical rotation was reported for the natural product so the absolute configuration could not be assigned.

## Conclusion

The total synthesis of diastereomer **22**, the enantiomer of the natural product micropyrone (**1**), was achieved in 9 linear steps (10% overall yield) without epimerization of the sensitive C6 position α to both the pyrone ring and the carbonyl. The synthesis of compound **28**, the (+)-enantiomer of the natural product ascosalipyrone, was achieved in 9 linear steps (6% overall yield), from the common aldehyde intermediate **11**. Compound **28** was isolated as an unequal mixture of diastereomers due to partial epimerization of C6 upon formation of the pyrone ring, but this epimerization did not occur during the synthesis of *ent*-micropyrone (**22**). The lack of epimerization in this case can be rationalized by the presence of the C4 methyl and the resulting increased $A^{1,3}$ strain that would be present in the planar enol epimerization intermediate.

## Experimental

### Ethyl (6*S*,7*S*,8*S*)-7-[(*tert*-butyl)dimethylsilyloxy]-5-hydroxy-2,4,6,8-tetramethyl-3-oxodecanoate (18)

To a stirred suspension of NaH (183 mg; 7.63 mmol) in THF (22 mL) at 0 °C was added ethyl 2-methyl-3-oxo-pentanoate (**17**) (690 mg; 4.36 mmol) and the resulting mixture was stirred at 0 °C for 10 min, before cooling to −10 °C. *n*-BuLi (2.73 mL; 1.6 M in hexanes; 4.36 mmol) was then added, with stirring at −10 °C for a further 10 min. The reaction mixture was cooled to −78 °C and a solution of aldehyde (**11**) (563 mg; 2.18 mmol) in THF (5 mL) was added dropwise *via* cannula and the reaction mixture was stirred at −78 °C for 1 h. The reaction was quenched by addition of sat. aq. $NH_4Cl$ (20 mL) and allowed to warm to rt. The mixture was extracted with $Et_2O$ (4 × 20 mL) and the combined organic extracts were washed with brine (40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Residual ethyl 2-methyl-3-oxo-pentanoate was removed under high vacuum and the crude product was filtered through a plug of buffered silica (100% $CH_2Cl_2$) to give a complex mixture of isomers of alcohol (**18**) (890 mg; 98%) as a clear oil. $^{1}H$ NMR (600 MHz, $CDCl_3$) $\delta$ 4.19–4.12 (2H, m), 3.97–3.77 (1.5H, m), 3.75, 3.73, 3.68 & 3.65 (4 × 0.25H, q, *J* = 7.2 Hz), 3.63 (0.5H, dd, *J* = 7.2, 3.0 Hz) 2.95 (0.5H, dq, *J* = 7.2, 6.6 Hz), 2.86 (2 × 0.25H, dq, *J* = 7.2, 6.6 Hz), 1.75–1.35 (3H, m), 1.32–1.29 (3H, m), 1.26–1.22 (3.75H, m), 1.18, 1.08 & 1.07 (3 × 0.75H, d, *J* = 7.2 Hz), 1.07–0.95 (1H, m), 0.92–0.83 (16.5H, m), 0.78 & 0.74 (2 × 0.75H, d, *J* = 7.2 Hz), 0.08–0.04 (6H, m) (OH not assigned); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 211.9, 211.8, 210.9, 210.0, 209.5, 170.6, 170.4, 170.4, 170.2, 170.1, 167.9, 84.5, 80.4, 80.0, 79.5, 79.1, 78.3, 77.0, 76.0, 75.7, 75.5, 75.3, 71.8, 71.2, 61.60, 61.53, 61.49, 61.47, 61.3, 54.4, 53.8, 52.7, 52.0, 51.8, 50.92, 50.87, 50.0, 49.9, 49.0, 48.8, 48.6, 47.5, 47.4, 47.0, 40.89, 40.87, 40.76, 40.6, 39.9, 39.7, 39.4, 39.0, 38.7, 38.3,

37.9, 37.1, 36.8, 35.5, 34.5, 33.8, 32.0, 30.4, 29.8, 29.5, 23.4, 22.8, 22.3, 18.53, 18.49, 18.45, 18.40, 18.38, 18.35, 16.5, 16.2, 15.8, 15.7, 15.6, 15.4, 15.24, 15.18, 15.0, 14.19, 14.17, 14.14, 14.0, 13.3, 13.2, 13.11, 13.05, 13.00, 12.9, 12.7, 12.55, 12.50, 12.41, 12.37, 12.35, 12.29, 12.23, 12.16, 12.0, 11.9, 11.7, 11.5, 10.5, 9.1, 9.0, 8.8, 8.4, 8.1, 7.8, 7.5, −3.30, −3.39, −3.40, −3.8, −4.00, −4.07, −4.11, −4.16, −4.20, −4.29, −4.31, −4.35.

### Ethyl (6*R*,7*S*,8*S*)-7-[(*tert*-butyl)dimethylsilyloxy]-2,4,6,8-tetramethyl-3,5-dioxodecanoate (19)

To a stirred solution of alcohol (**18**) (913 mg; 2.19 mmol) in $CH_2Cl_2$ (22 mL) at rt in the dark was added Dess–Martin periodinane (1.39 g; 3.29 mmol), followed immediately by addition of a $H_2O$–$CH_2Cl_2$ mixture (3.65 mL of sat. aq. $CH_2Cl_2$) and addition of the moist $CH_2Cl_2$ continued every 5 min for 1 h (*i.e.* 12 × 3.65 mL aliquots). The reaction mixture was stirred at rt for 2 days before diluting with $Et_2O$ (100 mL). Sat. aq. $NaHCO_3$ (60 mL) containing $Na_2S_2O_3{\cdot}5H_2O$ (7.7 g) was added to quench the reaction with stirring for 5 min. The layers were separated and the organic layer was washed with sat. aq. $NaHCO_3$ (60 mL) and brine (60 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was filtered through buffered silica (100% $CH_2Cl_2$) to afford tricarbonyl (**19**) (900 mg; 99%) as a clear oil. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 4.20–4.08 (2.5H, m), 4.04, 4.03 (2 × 0.25H, q, $J$ = 7.2 Hz), 3.95 (0.25H, dd, $J$ = 5.4, 3.6 Hz), 3.88–3.84 (0.5H, m), 3.83 (0.25H, dd, $J$ = 6.0, 3.6 Hz), 3.75–3.70 (0.5H, m), 3.62 (0.25H, q, $J$ = 7.2 Hz), 3.61 (0.25H, q, $J$ = 7.2 Hz), 2.91–2.86 (0.5H, m), 2.84 (0.25H, dq, $J$ = 6.6, 6.0 Hz), 2.78 (0.25H, dq, $J$ = 7.2, 6.0 Hz), 1.55–1.26 (5.5H, m), 1.25–1.16 (5.5H, m), 1.12–0.79 (1.5H, m), 1.06–1.03 (1.5H, m), 1.07–0.99 (1H, m), 0.88–0.83 (15H, m), 0.03 to −0.03 (6H, s); $^{13}$C NMR (151 MHz, $CDCl_3$) $\delta$ 210.5, 210.0, 209.1, 208.8, 207.0, 203.40, 203.37, 202.35, 202.29, 195.3, 195.1, 193.2, 192.0, 191.9, 171.0, 170.9, 170.1, 103.6, 103.4, 77.30, 77.27, 77.25, 76.7, 76.0, 75.8, 75.5, 75.4, 75.1, 61.64, 61.62, 61.56, 61.55, 61.29, 61.26, 60.9, 59.2, 58.8, 58.7, 57.5, 53.5, 52.3, 51.6, 50.8, 50.0, 49.8, 49.7, 49.4, 48.8, 48.5, 48.2, 46.1, 45.9, 44.04, 44.00, 42.4, 41.2, 41.10, 41.08, 41.02, 40.9, 40.78, 40.74, 40.71, 40.66, 37.8, 37.4, 37.1, 34.4, 33.7, 32.0, 30.9, 30.4, 29.8, 27.14, 26.12, 26.09, 26.07, 24.72, 24.69, 24.66, 24.59, 24.4, 24.3, 23.3, 18.43, 18.41, 18.39, 18.37, 16.9, 16.24, 16.16, 16.13, 16.09, 16.08, 16.06, 15.99, 15.92, 15.6, 15.5, 14.2, 14.14, 14.11, 14.10, 14.0, 13.9, 13.8, 13.6, 13.5, 13.4, 13.3, 13.18, 13.14, 13.10, 12.91, 12.86, 12.63, 12.57, 12.29, 12.24, 12.15, 12.11, 12.09, 12.04, 8.0, 7.7, 7.4, −3.82, −3.86, −3.94, −3.96, −4.04, −4.07, −4.10, −4.12.

### 6-[(1*R*,2*S*,3*S*)-2-[(*tert*-Butyl)dimethylsilyloxy]-1,3-dimethylpentyl]-4-hydroxy-3,5-dimethyl-2*H*-pyran-2-one (20)

To a stirred solution of tricarbonyl (**19**) (486 mg; 1.17 mmol) in benzene (12 mL) was added DBU (88 μL; 586 μmol) dropwise, and the resulting solution heated to 60 °C for 3 h. The reaction mixture was then cooled to 0 °C and quenched by addition of 1 M HCl (10 mL). The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed with brine (2 × 20 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. The resulting residue was triturated with hexanes to give α-pyrone (**20**) as a single isomer (193 mg; 45%) as colourless needles. $R_f$ = 0.27 (10% $Et_2O/CH_2Cl_2$); mp. 179–181 °C; $[\alpha]_D^{20}$ = −50.3 (c 0.80, MeOH); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 9.39 (1H, br s), 3.84 (1H, dd, $J$ = 9.0, 2.4 Hz), 2.98 (1H, dq, $J$ = 9.0, 6.6 Hz), 2.03 (3H, s), 1.99 (3H, s), 1.36–1.30 (1H, m), 1.28–1.21 (1H, m), 1.18 (3H, d, $J$ = 6.6 Hz), 0.91–0.88 (1H, m), 0.88 (9H, s), 0.86 (3H, d, $J$ = 7.2 Hz), 0.79 (3H, dd, $J$ = 7.8, 7.2 Hz), 0.02 (3H, s), 0.01 (3H, s); $^{13}$C NMR (151 Mz, $CDCl_3$) $\delta$ 167.1, 166.5, 161.1, 107.5, 98.5, 78.2, 40.8, 38.2, 26.2, 24.3, 18.4, 17.1, 16.0, 12.8, 10.0, 9.0, −3.8, −3.9; IR (KBr, cm$^{-1}$) 2961, 2933, 2874, 2859, 1680, 1659, 1573, 1543, 1462, 1379, 1343, 1256, 1177, 1153, 1124, 1080, 1061, 1032, 1006, 936, 854, 836, 777, 758, 695, 670, 619, 514, 472.

### 6-[(1*R*,2*S*,3*S*)-2-Hydroxy-1,3-dimethylpentyl]-4-hydroxy-3,5-dimethyl-2*H*-pyran-2-one (21)

To a stirred solution of TBS–ether (**20**) (193 mg; 523 μmol) in a 1 : 1 mixture of $CH_3CN$–$CH_2Cl_2$ (26 mL) at rt was added 40% aq. HF (2.20 mL) and the resulting mixture stirred at rt for 3.5 h. The reaction was quenched by addition of $H_2O$ (25 mL) and the mixture was extracted with EtOAc (3 × 40 mL). The combined organic extracts were dried ($Na_2SO_4$) and concentrated *in vacuo* to give a white slurry, which was triturated with acetone to afford alcohol (**21**) (126 mg; 95%) as clear needles. $R_f$ = 0.50 (100%, EtOAc); mp. 143–145 °C; $[\alpha]_D^{20}$ = −108.6 (*c* 1.05, MeOH); $^1$H NMR (600 MHz, $CD_3OD$) $\delta$ 5.13 (1H, br s), 3.63 (1H, dd, $J$ = 9.0, 3.6 Hz, C*H*OH), 3.08 (1H, dq, $J$ = 9.0, 6.6 Hz), 1.99 (3H, s), 1.92 (3H, s), 1.46 (1H, ddq, $J$ = 13.2, 7.8, 3.0 Hz), 1.29 (1H, s), 1.27 (3H, d, $J$ = 7.2 Hz), 1.20 (1H, m), 1.09 (1H, ddq, $J$ = 13.2, 9.6, 7.2 Hz), 0.94 (3H, d, $J$ = 6.6 Hz), 0.84 (3H, dd, $J$ = 7.8, 7.2 Hz); $^{13}$C NMR (151 Mz, $CD_3OD$) $\delta$ 168.4, 168.1, 162.0, 109.2, 98.9, 78.9, 39.6, 39.3, 23.8, 17.0, 15.4, 12.4, 10.0, 8.8; IR (KBr, cm$^{-1}$) 3188, 2962, 2930, 2878, 1662, 1617, 1566, 1460, 1381, 1273, 1213, 1144, 1100, 1031, 996, 963, 944, 881, 765, 707, 672, 579, 520, 473; HRESIMS calculated for $C_{14}H_{22}O_4Na^+$: 277.1410; found 277.1417.

### 6-[(1*S*,3*S*)-1,3-Dimethyl-2-oxopentyl]-4-hydroxy-3,5-dimethyl-2*H*-pyran-2-one (22)

To a stirred solution of alcohol (**21**) (105 mg; 439 μmol) in acetone (11 mL) at 0 °C was added Jones reagent (760 μL) dropwise. The reaction mixture was warmed to rt for 10 min and quenched by addition of isopropanol (600 μL), followed by addition of $NaHCO_3$ (600 mg). The solution was filtered and the filtrate was concentrated *in vacuo*. The residue was taken up in $Et_2O$ (10 mL), washed with $H_2O$ (10 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. The crude product was triturated with hexanes to remove impurities, giving 6-[(1*S*,3*S*)-1,3-dimethyl-2-oxopentyl]-4-hydroxy-3,5-dimethyl-2*H*-pyran-2-one (**22**) (57.5 mg; 55%) as colourless needles. $R_f$ = 0.46 (100% EtOAc); mp. 152–154 °C; $[\alpha]_D^{20}$ = +28.8 (*c* 1.36, MeOH); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 8.84 (1H, br s), 3.83 (1H, q), 2.58 (1H, ddq, $J$ = 13.2, 7.2, 6.6 Hz), 2.02 (3H, s), 1.99 (3H, s), 1.59 (1H, ddq, $J$ = 13.8, 7.2, 6.6 Hz,), 1.36 (3H, d, $J$ = 7.2 Hz), 1.34 (1H, m), 0.98 (3H, d, $J$ = 7.2 Hz), 0.81 (3H, t, $J$ = 7.2 Hz,

$CH_2CH_3$); $^{13}C$ NMR (151 Mz, $CDCl_3$) $\delta$ 210.9, 166.4, 165.7, 155.8, 109.6, 99.6, 48.4, 45.5, 27.1, 16.3, 13.5, 11.7, 10.1, 8.9; IR (KBr, $cm^{-1}$) 3209, 2934, 2967, 1722, 1662, 1635, 1576, 1455, 1380, 1212, 1176, 1124, 1079, 1041, 971, 871, 755, 478; HRESIMS calculated for $C_{14}H_{20}O_4Na^+$: 275.1254; found: 274.1265.

**Ethyl (6*S*,7*S*,8*S*)-7-[(*tert*-butyl)dimethylsilyloxy]-5-hydroxy-2,6,8-trimethyl-3-oxodecanoate (25)**

To a stirred suspension of NaH (170 mg; 7.07 mmol) in THF (20 mL) at 0 °C was added ethyl-2-methylacetoacetate (572 μL; 4.04 mmol) and the resulting mixture was stirred at 0 °C for 10 min, before cooling to −10 °C. *n*-BuLi (2.53 mL; 1.6 M in hexanes; 4.04 mmol) was then added, with stirring at −10 °C for a further 10 min. The reaction mixture was cooled to −78 °C and a solution of aldehyde (**11**) (522.8 mg; 2.02 mmol) in THF (5 mL) was added dropwise *via* cannula and the reaction mixture was stirred at −78 °C for 1 h. The reaction was quenched by addition of sat. aq. $NH_4Cl$ (20 mL) and allowed to warm to rt. The mixture was extracted with $Et_2O$ (4 × 20 mL) and the combined organic extracts were washed with brine (40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. Residual ethyl-2-methylacetoacetate was removed under high vacuum and the residue was filtered through a plug of buffered silica (100% $CH_2Cl_2$) to give a complex mixture of isomers of alcohol (**25**) (785 mg; 96%) as a yellow oil. $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 4.18–4.14 (2H, m), 4.08–4.04 (0.5H, m), 3.91–3.85 (0.5H, m), 3.84 (0.5H, ddd, $J$ = 6.0, 3.6, 1.8 Hz), 3.68 (0.5H, m), 3.55, 3.54, 3.51, 3.51 (4 × 0.25H, q, $J$ = 7.2 Hz), 2.81 (0.25H, dd, $J$ = 16.8, 2.4 Hz), 2.77 (0.25H, dd, $J$ = 17.4, 2.4 Hz), 2.72 (0.25H, dd, $J$ = 17.4, 5.4 Hz), 2.72 (0.25H, dd, $J$ = 16.8, 2.4 Hz), 2.65 (0.25H, dd, $J$ = 16.8, 8.4 Hz), 2.64 (0.25H, dd, $J$ = 17.4, 3.6 Hz), 2.59 (0.25H, dd, $J$ = 15.6, 9.0 Hz), 2.53 (0.25H, dd, $J$ = 17.4, 9.0 Hz), 1.68–1.50 (1H, m), 1.58–1.49 (1H, m), 1.50–1.35 (1H, m), 1.32 (0.75H, d, $J$ = 7.2 Hz), 1.31 (1.5H, d, $J$ = 7.2 Hz), 1.30 (0.75H, d, $J$ = 7.2 Hz), 1.24 (3H, t, $J$ = 7.2 Hz), 1.11–0.99 (1H, m), 0.89 (1.5H, d, $J$ = 7.2 Hz), 0.88–0.85 (13.5H, m), 0.83 (1.5H, d, $J$ = 7.2 Hz), 0.76 (1.5H, d, $J$ = 6.6 Hz), 0.06 (1H, s), 0.06 (1H, s), 0.04 (2H, s) 0.04 (2H, s), (OH not assigned); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 207.4, 207.2, 206.64, 206.56, 170.41, 170.35, 170.32, 77.6, 77.5, 75.5, 70.8, 70.5, 69.8, 69.7, 61.54, 61.51, 53.7, 53.52, 53.48, 53.45, 46.6, 46.5, 46.3, 46.1, 43.9, 40.9, 40.8, 40.7, 40.6, 39.67, 39.66, 39.64, 39.58, 38.8, 26.2, 26.1, 25.9, 25.71, 25.66, 23.34, 23.33, 23.32, 22.8, 22.3, 18.45, 18.42, 18.41, 15.89, 15.87, 15.38, 15.36, 14.2, 12.8, 12.68, 12.63, 12.60, 12.4, 12.1, 11.4, 9.9, 9.8, −3.5, −3.99, −4.02, −4.11, −4.13, −4.22, −4.24.

**Ethyl (6*R*,7*S*,8*S*)-7-[(*tert*-butyl)dimethylsilyloxy]-2,6,8-trimethyl-3,5-dioxodecanoate (30)**

To a stirred solution of alcohol (**25**) (762 mg; 1.89 mmol) in $CH_2Cl_2$ (19 mL) at rt in the dark was added Dess–Martin periodinane (1.20 g; 2.84 mmol), followed immediately by addition of a $H_2O$–$CH_2Cl_2$ mixture (3.15 mL of sat. aq. $CH_2Cl_2$) and addition of the moist $CH_2Cl_2$ continued every 5 min for 1 h (*i.e.* 12 × 3.15 mL aliquots). The reaction mixture was stirred at rt for 2 days before diluting with $Et_2O$ (100 mL). Sat. aq. $NaHCO_3$ (60 mL) containing $Na_2S_2O_3{\cdot}5H_2O$ (7.7 g) was added to quench the reaction with stirring for 5 min. The layers were separated and the organic layer was washed with sat. aq. $NaHCO_3$ (60 mL) and brine (60 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was filtered through buffered silica (100% $CH_2Cl_2$) to afford tricarbonyl (**30**) (720 mg; 95%) as a yellow oil. Enol tautomer $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 5.58 (0.5H, s), 5.57 (0.5H, s), 4.14 (2H, q, $J$ = 7.2 Hz), 3.80 (1H, dd, $J$ = 5.4, 4.8 Hz), 3.34 (2 × 0.5H, q, $J$ = 7.2 Hz), 2.48 (1H, dq, $J$ = 7.2, 6.6 Hz), 1.50–1.36 (1H, m), 1.34 (2 × 1.5H, $J$ = 7.2 Hz), 1.32–1.16 (1H, m), 1.22 (3H, t, $J$ = 7.2 Hz), 1.15–1.00 (1H, m), 1.08 (3H, d, $J$ = 7.2 Hz), 0.89–0.80 (15H, m), −0.01 (3H, s), −0.07 (3H, s), (enol OH not assigned); $^{13}C$ NMR (151 MHz, $CDCl_3$) $\delta$ 195.07, 194.96, 193.2, 193.0, 170.8, 169.3, 99.3, 98.1, 77.4, 77.04, 77.01, 75.2, 73.8, 73.2, 72.7, 61.35, 61.34, 53.5, 49.7, 49.6, 44.7, 43.9, 43.7, 41.4, 40.6, 38.8, 34.6, 33.2, 30.9, 29.8, 26.1, 25.03, 25.01, −4.1, −4.23, −4.26.

**6-[(1*R*,2*S*,3*S*)-2-[(*tert*-Butyl)dimethylsilyloxy]-1,3-dimethylpentyl]-4-hydroxy-3-methyl-2*H*-pyran-2-one (26) and 6-[(1*S*,2*S*,3*S*)-2-[(*tert*-butyl)dimethylsilyloxy]-1,3-dimethylpentyl]-4-hydroxy-3-methyl-2*H*-pyran-2-one (27)**

To a stirred solution of tricarbonyl (**30**) (337.2 mg; 842 μmol) in benzene (8.4 mL) was added DBU (63 μL) dropwise, and the resulting solution heated to 60 °C for 3 h. The reaction mixture was then cooled to 0 °C and quenched by addition of 1 M HCl (10 mL). The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed with brine (2 × 20 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. The resulting residue was triturated with hexanes to remove any impurities, resulting in a 78 : 22 mixture of α-pyrones (**26**) and (**27**) (75.1 mg; 25%) as white needles. $R_f$ = 0.31 (10% $Et_2O/CH_2Cl_2$); mp. 153–155 °C; $[\alpha]_D^{20}$ = +93.2 (*c* 0.81, MeOH); $^1H$ NMR (600 MHz, $CDCl_3$) major isomer: $\delta$ 10.41 (1H, br s), 6.22 (1H, s), 3.82 (1H, dd, $J$ = 4.8, 4.2 Hz), 2.72 (1H, dq, $J$ = 6.6, 5.4 Hz), 1.96 (3H, s), 1.50–1.42 (1H, m), 1.47–1.39 (1H, m), 1.18 (3H, d, $J$ = 6.6 Hz),1.01–0.94 (1H, m), 0.89 (3H, d, $J$ = 7.2 Hz), 0.86 (3H, dd, $J$ = 7.8, 7.2 Hz) 0.85 (9H, s), 0.00 (3H, s), −0.15 (3H, s); minor isomer: $\delta$ 10.41 (1H, br s), 6.24 (1H, s), 3.80 (1H, dd, $J$ = 7.2, 3.6 Hz), 2.76–2.71 (1H, m), 1.96 (3H, s), 1.57–1.51 (1H, m), 1.47–1.39 (1H, m), 1.16 (3H, d, $J$ = 7.2 Hz), 1.00–0.94 (1H, m), 0.88 (3H, d, $J$ = 7.2 Hz), 0.86 (3H, dd, $J$ = 7.8, 7.2 Hz) 0.81 (9H, s), 0.01 (3H, s), −0.19 (3H, s); $^{13}C$ NMR (151 Mz, $CDCl_3$) major isomer: $\delta$ 168.6, 167.4, 166.1, 101.4, 98.8, 77.0, 41.2, 40.5, 26.2, 25.2, 18.3, 15.5, 13.6, 12.4, 8.3, −3.9, −4.4; minor isomer: $\delta$ 168.7, 167.5, 165.8, 102.0, 98.9, 77.8, 43.1, 38.9, 26.1, 24.0, 18.4, 16.0, 15.6, 12.4, 8.3, −3.9, −4.7; IR (KBr, $cm^{-1}$) 3153, 2962, 2890, 2859, 2704, 1653, 1590, 1456, 1410, 1372, 1293, 1252, 1173, 1150, 1120, 1084, 1054, 966, 937, 864, 835, 774, 754, 675, 645, 534, 483.

**6-[(1*R*,2*S*,3*S*)-2-Hydroxy-1,3-dimethylpentyl]-4-hydroxy-3-methyl-2*H*-pyran-2-one (31) and 6-[(1*S*,2*S*,3*S*)-2-hydroxy-1,3-dimethylpentyl]-4-hydroxy-3-methyl-2*H*-pyran-2-one (32)**

To a stirred solution of a 78 : 22 mixture of TBS–ethers (**26**) and (**27**) (98.7 mg; 297 μmol) in a 1 : 1 mixture of $CH_3CN$–$CH_2Cl_2$

(15 mL) at rt was added 40% aq. HF (1.30 mL) and the resulting mixture was stirred at rt for 3.5 h. The reaction was quenched by addition of $H_2O$ (15 mL) and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracted were dried ($Na_2SO_4$) and concentrated *in vacuo* to give a white slurry, which was triturated with acetone to afford alcohol (**31**) (as a mixture with its C6 epimer **32**) (66.9 mg; 96%) as a white powder. $R_f$ = 0.46 (100%, EtOAc); mp. 212–214 °C; $[\alpha]_D^{20}$ = +51.4 (*c* 0.92, MeOH); $^1$H NMR (600 MHz, $CD_3OD$) major isomer: $\delta$ 6.06 (1H, s), 5.24 (1H, br s), 3.57 (1H, dd, *J* = 6.6, 5.4 Hz), 3.45 (1H, s), 2.71 (1H, dq, *J* = 7.2, 6.6 Hz), 1.85 (3H, s), 1.68 (1H, ddq, *J* = 13.2, 7.8, 3.0 Hz), 1.40–1.35 (1H, m), 1.27 (3H, d, *J* = 6.6 Hz), 1.17–1.10 (1H, m), 0.92 (3H, d, *J* = 6.6 Hz), 0.89 (3H, dd, *J* = 7.8, 7.2 Hz); minor isomer: $\delta$ 6.11 (1H, s), 5.24 (1H, br s), 3.51 (1H, dd, *J* = 7,2, 4.8 Hz), 3.35 (1H, s), 2.80–2.75 (1H, m), 1.85 (3H, s), 1.57 (1H, ddq, *J* = 13.2, 7.8, 3.0 Hz), 1.55–1.49 (1H, m), 1.20 (3H, d, *J* = 7.2 Hz), 1.17–1.10 (1H, m), 0.98 (3H, d, *J* = 7.2 Hz), 0.92 (3H, dd, *J* = 7.8, 7.2 Hz); $^{13}$C NMR (151 Mz, $CDCl_3$) major isomer: $\delta$ 169.1, 168.1, 167.0, 101.4, 99.1, 77.4, 42.0, 39.1, 25.1, 16.0, 12.1, 11.7, 8.2; minor isomer: $\delta$ 169.3, 168.2, 167.4, 102.2, 99.1, 78.4, 43.0, 38.2, 23.5, 16.6, 16.3, 11.9, 8.2; IR (KBr, $cm^{-1}$) 3149, 1973, 2924, 2882, 2729, 1682, 1660, 1593, 1462, 1414, 1391, 1299, 1270, 1233, 1178, 1114, 1076, 1045, 974, 957, 935, 826, 748, 680, 634, 535; HRESIMS calculated for $C_{13}H_{20}O_4Na^+$: 263.1254; found: 263.1263.

### 6-[(1*S*,3*S*)-1,3-Dimethyl-2-oxopentyl]-4-hydroxy-3-methyl-2*H*-pyran-2-one (28)

To a stirred solution of alcohol (**31**) (as a mixture with its C6 epimer **32**) (56.8 mg; 236 μmol) in acetone (6 mL) at 0 °C was added Jones reagent (410 μL) dropwise. The reaction mixture was warmed to rt for 10 min and quenched by addition of isopropanol (300 μL), followed by addition of $NaHCO_3$ (300 mg). The solution was filtered and the filtrate was concentrated *in vacuo*. The residue was taken up in $Et_2O$ (10 mL), washed with $H_2O$ (10 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. The crude product was triturated with hexanes to remove impurities, giving 6-[(1*S*,3*S*)-1,3-dimethyl-2-oxopentyl]-4-hydroxy-3-methyl-2*H*-pyran-2-one (**28**) (31.3 mg; 56%) as a yellow powder. $R_f$ = 0.54 (100% EtOAc); mp. 115–117 °C; $[\alpha]_D^{20}$ = +60.7 (c 1.57, MeOH); $^1$H NMR (600 MHz, $CDCl_3$) major isomer: $\delta$ 9.91 (1H, br s), 6.25 (1H, s), 3.80 (1H, q, *J* = 7.2 Hz), 2.70 (1H, ddq, *J* = 13.8, 7.2, 6.6 Hz), 1.94 (3H, s), 1.67 (1H, ddq, *J* = 13.8, 7.8, 6.6 Hz), 1.38 (1H, m), 1.36 (3H, d, *J* = 7.2 Hz), 1.05 (3H, d, *J* = 6.6 Hz), 0.85 (3H, dd, *J* = 7.8, 7.2 Hz); minor isomer: $\delta$ 9.91 (1H, br s), 6.25 (1H, s), 3.81 (1H, q, *J* = 7.2 Hz), 2.68 (1H, m), 1.94 (3H, s), 1.68 (1H, m), 1.35 (3H, d, *J* = 7.2 Hz), 1.35 (1H, m), 1.07 (3H, d, *J* = 7.2 Hz), 0.80 (3H, t, *J* = 7.2 Hz); $^{13}$C NMR (151 Mz, $CDCl_3$) major isomer: $\delta$ 211.6, 167.8, 166.5, 160.8, 101.8, 99.9, 49.4, 47.1, 26.1, 16.0, 14.4, 11.7, 8.3; minor isomer: $\delta$ 211.4, 167.8, 166.4, 160.7, 101.8, 99.9, 49.2, 47.0, 25.8, 16.5, 14.6, 11.7, 8.3; IR (KBr, $cm^{-1}$) 2970, 2933, 2879, 2668, 1718, 1665, 1632, 1569, 1459, 1271, 1242, 1181, 1141, 1099, 1028, 994, 949, 936, 859, 757, 617, 565, 531; HRESIMS calculated for $C_{13}H_{18}O_4Na^+$: 261.1097; found: 261.1109.

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