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# Synthetic studies towards oxygenated and unsaturated furanocembranoid macrocycles. Precursors to plumarellide, rameswaralide and mandapamates

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ABSTRACT

A new approach to the synthesis of oxygenated furanocembranoids, exemplified by danielid **3**, is described. The approach features an intermolecular Knoevenagel-type condensation together with an intramolecular aldolisation to elaborate the furan and the lactone rings, respectively, in the initial target compound **14**. Efforts to isomerise the C13–C14 double bond, or to introduce an alkene bond at C11–C12 in **14**, leading to structures **3** and **8**, respectively, are described.



Gorgonian octocorals are a hugely rich source of biologically interesting macrocyclic ('cembranoid') diterpenes, many of which are based on the furanobutenolide motif **1**, carrying an array of oxygenation patterns, for example, **2**, **3** and **4**.[1] Furthermore, these oxygenated macrocycles co-occur with an interesting variety of carbocyclic structures, viz, mandapamate (**5**),[2] plumarellide (**6**)[3] and rameswaralide (**7**),[4] which are related as products resulting from transannular cyclisations in the former. In earlier publications we outlined our interest in examining the biosynthetic interrelationships within these groups of natural products in octocorals by simulating some of the aforementioned transannular processes in vitro.[5,6] With the limited availability of oxygenated and unsaturated furanobutenolide cembranoids from Nature, such investigations have been hampered by the dearth of synthetic routes to structures akin to **2**, **3** and **4**.[7,8] In this Letter, we present a synthetic approach to the natural product danielid **3**[9] and to the vinylbutenolide-based furanocembrane **8**, which we believe are implicated in the biosynthesis of the polycyclic natural products **5**, **6** and **7**.

Our synthetic strategy towards **3** and **8** was based on a Knoevenagel-type condensation between the epoxyaldehyde **9** and the β-ketoester **10** leading to **11** (Scheme 1), which should undergo cyclisation in situ producing the substituted furanmethanol **12**.[10] We next planned to modify the functionality in **12** to the α-silyloxyaldehyde **13**, and then to carry out an intramolecular aldolisation, with simultaneous lactone ring formation producing the macrocyclic cembranoid **14**.[10] Isomerisation of the C13–C14 alkene bond in **14** to the C12–C13 position and dehydration between C11 and C12 would then lead to precursors for elaboration to the target compounds **3** and **8**, respectively.

Thus, addition of the acetylenic anion produced from propargyl alcohol to the known homochiral ketone **15**[11] first gave the corresponding *t*-alcohol **16** as a 1:1 mixture of diastereoisomers. Reduction of the separated diastereomer **16**[12] with $LiAlH_4$ next led to the *E*-allylic alcohol **17** which was then converted into the epoxide **18** using Sharpless conditions (Scheme 2). Oxidation of the primary alcohol group in **18**, using Dess–Martin periodinane (DMP), finally gave the epoxyaldehyde **9**. The substituted β-keto ester **10** was synthesised in five steps from the known homochiral γ-unsaturated ester **19** derived from (+)-carvone.[13] Reduction of **19**, using DIBAL-H at −78 °C, gave the corresponding aldehyde which, in a Knoevenagel reaction with malonic acid in DMSO at 100 °C[14] led to the β,γ-unsaturated carboxylic acid **20a**. Esterification of **20a** to **b**, followed by deprotection of the acetal and treatment of the resulting aldehyde **21** with ethyl diazoacetate in the presence of $SnCl_2$, then gave the β-keto ester **10** in excellent yield.

When a solution of the epoxyaldehyde **9** and the β-keto ester **10** in THF containing acetic acid was treated with a catalytic amount of piperidine, work-up and chromatography gave the substituted furan **12** in 50% yield (Scheme 3).[15] Protection of the vicinal diol unit in **12** as the acetonide followed by selective deprotection of the mono-substituted acetonide in the product **22** next led to the diol **23a**. Bis-silylation of the vicinal diol **23a**, followed by regioselective desilylation of the primary alcohol silyl ether in **23a**, then produced the alcohol **23b**, which could be smoothly oxidised, using DMP, to the key α-silyloxyaldehyde intermediate **13**. Treatment of **13** with LiHMDS–LiCl in THF at −78 °C resulted in intramolecular aldolisation to **24** accompanied by in situ lactonisation and silyl group migration leading to a single diastereoisomer of the furanocembranoid **14** in 51% yield after chromatography.[16] The relative stereochemistry of the groups around the lactone ring in **14** was established by measurement of the NOE enhancements in the $^1H$ NMR spectrum of the desilylated derivative, produced from **14** using HF-pyridine in pyridine and THF.[17]

Our plan now was to isomerise the C13–C14 double bond in **14** and to also carry out an E1cb elimination of the C11-oxy group in **14** leading to precursors to the targets **3** and **8**, respectively. Each of these transformations, however, turned out to be very problematic.

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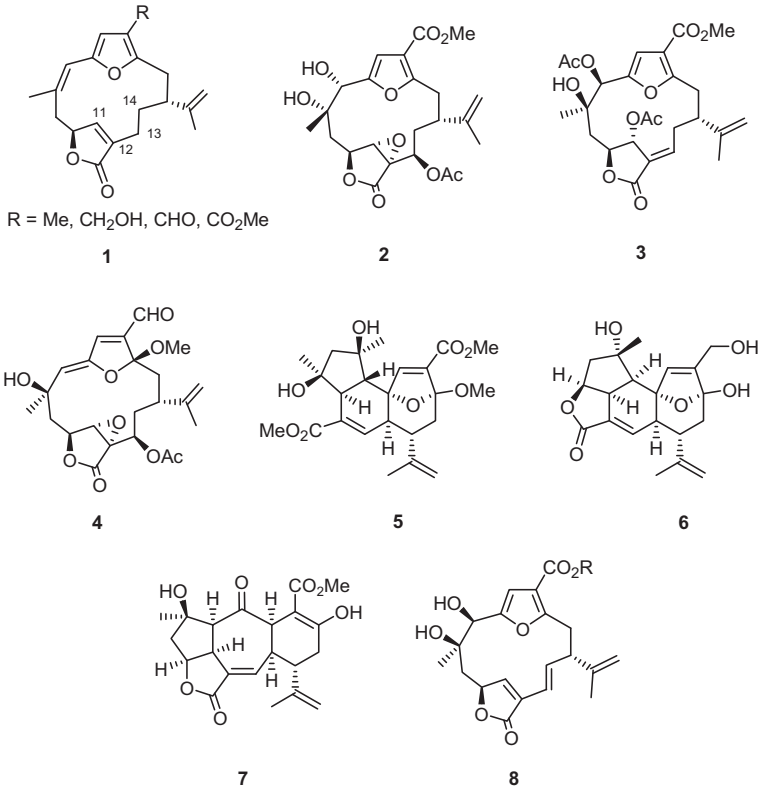
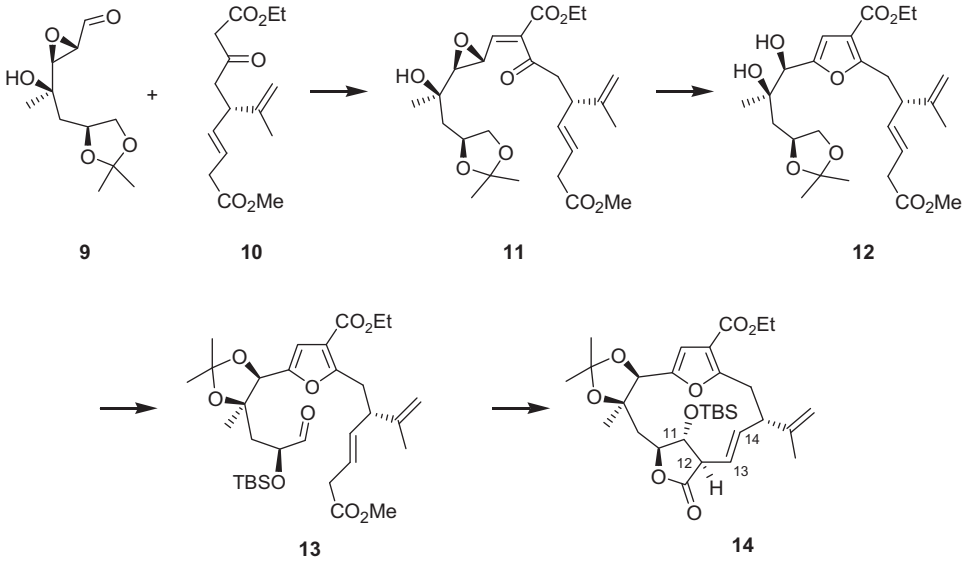
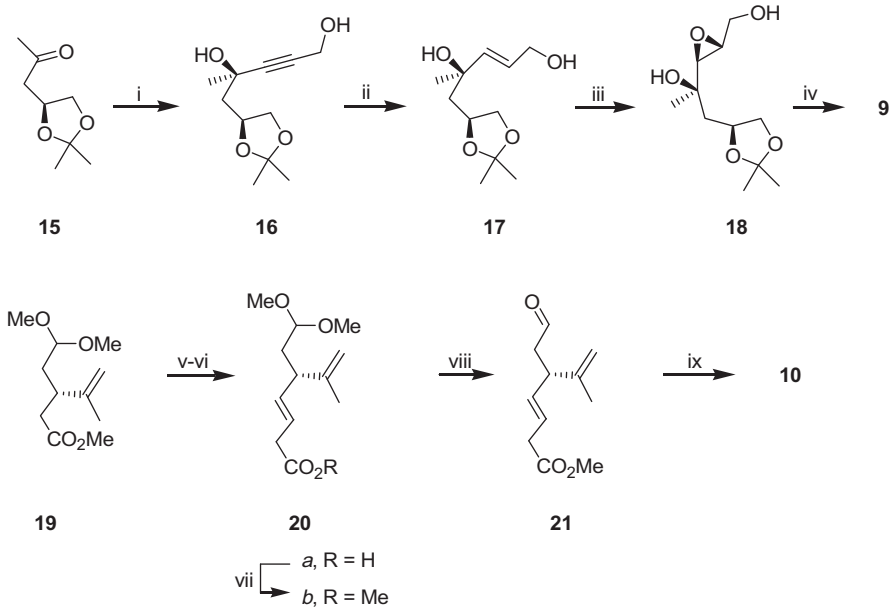



Thus, treatment of **14** with a range of bases (i.e., DBU, pyridine, LiHMDS-HMPA) and a variety of acids (e.g., TFA, HF-pyridine, PPTS, HCl, HOAc-pyridine) gave no evidence of isomerisation of the C13–C14 alkene to the corresponding C12–C13 alkene isomer or to the formation of a vinylbutenolide product. We surmised that the failure of these reactions was associated with restrictions in conformation of the rigid macrocyclic ring in **14**. Accordingly, we removed the acetonide group in **14**, using $H_2O$/HOAc (1:9), and then deprotected the silyl ether group in the resulting diol **25**, using TBAF, leading to the triol **26**. Finally, we prepared the bis-acetate **27**[18] from the triol **26**, which is an alkene positional isomer of danielid **3**, isolated recently from the soft coral *Sinularia asterolabata*.[9] Much to our chagrin, however, similar to **14**, we were not able to elaborate **27** to its C12–C13 alkene isomer or to the C7 acetate of the vinylbutenolide **8** (R = Et) under a range of conditions.

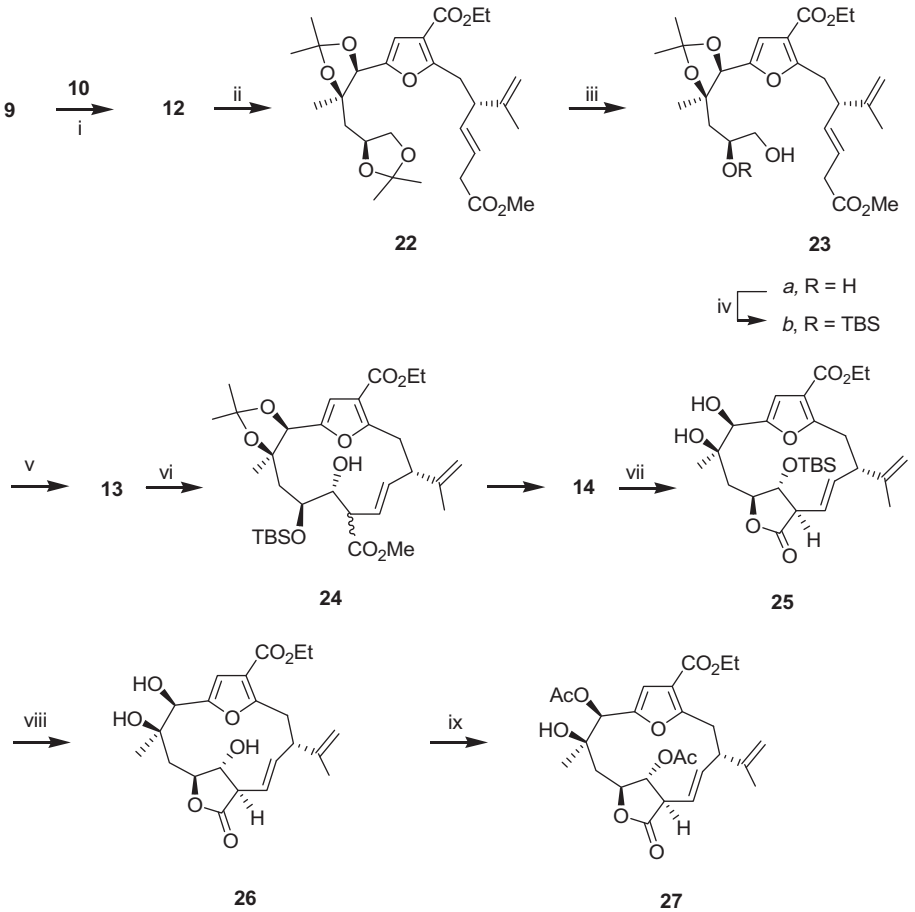
In summary, we have developed a concise synthetic route to a variety of C7, C8 and C11 oxygenated furanolactone-based cembranoids, using a strategy based on a Knoevenagel-type condensation and an aldolisation to incorporate the furan and the lactone rings, respectively. This new strategy has led to a synthesis of the C13–




**Scheme 1.** Synthetic strategy towards the furanocembranes **3** and **8**.




**Scheme 2.** Synthesis of the key intermediates **9** and **10**. Reagents and conditions: (i) $HCCCH_2OH$, BuLi (2 equiv), THF, −40 °C to rt, 70%, then chromatographic separation; (ii) $LiAlH_4$, THF, 0 °C to rt, 18 h, 82%; (iii) L-(+)-DET, $Ti(OPr\text{-}i)_4$, *t*-BuOOH, 4 Å MS, $CH_2Cl_2$, −20 °C to −5 °C, 4 h, 83%; (iv) DMP, $NaHCO_3$, $CH_2Cl_2$, 0 °C to rt, 1 h, 85%; (v) *i*-$Bu_2AlH$, toluene, −78 °C, 85–90%; (vi) $CH_2(CO_2H)_2$, piperidine–HOAc, DMSO, 100 °C, 4 h, 60%; (vii) MeOH, *p*-TSA, $(MeO)_3CH$, 36 h, 88%; (viii) 1 M HCl, $Me_2CO$, 40 °C, 2 h, 94%; (ix) $EtO_2CCHN_2$, $SnCl_2$, $CH_2Cl_2$, rt, 8 h, 90%.




**Scheme 3.** Reagents and conditions: (i) **10**, piperidine (cat.), THF–HOAc, rt, 1.5 h, then 55 °C, 4 h, 50%; (ii) $Me_2C(OMe)_2$, PPTS (cat.), reflux, 1 h, 40% over two steps; (iii) $H_2O$/HOAc (1:12), 50 °C, 2.5 h, 74%; (iv) TBSCl, imidazole, DMF, rt, 18 h, 90% then HF-pyridine, pyridine-THF, rt, 5 h, 49%; (v) DMP, $NaHCO_3$, $CH_2Cl_2$, rt, 1 h, 91%; (vi) LiHMDS, LiCl, THF, −78 °C, 1 h, rt, 18 h, 51%; (vii) $H_2O$/HOAc (1:9), 100 °C, 18 h, 98%; (viii) TBAF, THF, 0 °C to rt, 1 h, 90%; (ix) $Ac_2O$/pyridine (1:2), rt, 18 h, 65%.

C14 alkene positional isomer **27** of the natural product danielid **3**, but efforts to elaborate the vinylbutenolide **8** (R = Et), a purported biosynthetic precursor to the polycycles **5**, **6** and **7**, from **14** and **27** have so far been thwarted. An alternative strategy towards a synthesis of the vinylbutenolide-based furanocembrane **8** is in progress in our laboratory, which will be reported in due course.

## Acknowledgement

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8. For synthetic routes which have led to C13 and C14 oxygenated furanobutenolides cembranes, see: (a) Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993**, *58*, 165–169; (b) Cases, M.; Turiso, F. G. L.; Hadjisoteriou, M. S.; Pattenden, G. *Org. Biomol. Chem.* **2005**, *3*, 2786–2804; (c) Cases, M.; Turiso, F. G. L.; Pattenden, G. *Synlett* **2001**, 1869–1872.
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10. For a model study of these conversions, see Ref. 6a.
11. (a) Saito, S.; Hasegawa, T.; Inaba, N.; Nishida, R.; Fujii, T.; Nomizu, S.; Muriwake, T. *Chem. Lett.* **1984**, 1389–1392; (b) Doroh, B.; Sulikowski, G. A. *Org. Lett.* **2006**, *8*, 903–906.
12. The stereochemistry of **16** was established by chemical means followed by analysis of $^1$H NMR data. Thus, reaction of the epimeric *t*-alcohol with *p*-methoxybenzaldehyde dimethyl acetal (camphorsulfonic acid, $CH_2Cl_2$, 0 °C to rt, 18 h) resulted in facile conversion into the corresponding *p*-methoxydimethyl acetal in 78% yield. By contrast, the alcohol **16** failed to react with *p*-methoxybenzaldehyde dimethyl acetal under the same reaction conditions. This difference in reactivity between the epimeric *t*-alcohols is associated with the relatively small steric bulk of the alkyne group compared to the methyl group at the tertiary centre in **16**. cf Ref. 11b.
    The diastereoisomer **16** has the same stereochemistry at the *t*-hydroxy centre as in mandapamate (**5**) and rameswaralide (**7**), but is epimeric with the same centre in plumarellide (**6**).
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15. For an early example of this tandem Knoevenagel condensation–cyclisation of α-epoxy aldehydes to give furanmethanols, see: Williams, P. H.; Payne, G. B.; Sullivan, W. J.; Van Ess, P. R. *J. Am. Chem. Soc.* **1960**, *82*, 4883–4888.
16. For an earlier study of this reaction from our laboratory, see Ref. 6a.
17. The cembrane **14** was obtained as a colourless oil: $\delta_H$ (400 MHz, $CDCl_3$) 0.04 (3H, s, SiC*H*$_3$), 0.07 (3H, s, SiC*H*$_3$), 0.83 (9H, s, SiC(C*H*$_3$)), 1.29 (3H, s, C*H*$_3$), 1.33 (3H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.45 (3H, s, C*H*$_3$), 1.51 (1H, dd, *J* 15.7 and 1.9 Hz, C*H*HCH($O_2$C)), 1.61 (3H, s, C*H*$_3$), 1.70 (3H, t(br), *J* ~1 Hz, C*H*$_3$C=CH$_2$), 2.27 (1H, dd, *J* 15.7 and 7.2 Hz, CH*H*CH($O_2$C)), 3.11 (1H, dd, *J* 15.5 and 4.0 Hz, C*H*HFur), 3.19–3.23 (1H, m, C*H*-C(Me)=CH$_2$), 3.30–3.36 (1H, m, CH=CHC*H*$CO_2$R), 3.46 (1H, dd, *J* 15.5 and 8.2 Hz, CH*H*Fur), 4.26 (2H, q, *J* 7.2 Hz, $CO_2CH_2CH_3$), 4.56 (1H, s(br), =C*H*H), 4.57–4.62 (2H, m(AB), C*H*(OTBS)C*H*$O_2$C), 4.80 (1H, s, FurC*H*(OR)), 4.85 (1H, app. quint, *J* 4 × ~1.5 Hz, =CH*H*), 5.44 (1H, d(AB)dd, *J* 16.5, 3.5 and 1.9 Hz, C*H*=CH), 5.96 (1H, d(AB)dd, *J* 16.5, 5.4 and 2.3 Hz, CH=C*H*), 6.61 (1H, s, Fur*H*); $\delta_C$ (100 MHz, $CDCl_3$) −5.03 ($CH_3$), −4.99 ($CH_3$), 14.3 ($CH_3$), 17.9 (C), 21.7 ($CH_3$), 25.2 ($CH_3$), 25.6 (3$CH_3$), 27.4 ($CH_3$), 28.2 ($CH_3$), 31.2 ($CH_2$), 39.4 ($CH_2$), 45.6 (CH), 47.8 (CH), 60.3 ($CH_2$), 71.5 (CH), 78.8 (CH), 81.1 (CH), 82.7 (C), 110.3 (C), 110.7 (CH), 112.8 ($CH_2$), 115.4 (C), 123.4 (CH), 134.3 (CH), 144.7 (C), 148.3 (C), 160.8 (C), 163.6 (C), 174.9 (C); *m*/*z* (ESI) 597.2830 ($C_{31}H_{46}O_8SiNa^+$ requires 597.2854).
    Desilylation of **14** (HF-pyridine, pyridine, THF, 40 °C, 2 days) gave the corresponding *sec*-alcohol, in quantitative yield as an almost colourless oil, $\delta_H$ (400 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1 Hz, $CO_2CH_2CH_3$), 1.47 (3H, s, C*H*$_3$), 1.48 (3H, s, C*H*$_3$), 1.60 (3H, s, C*H*$_3$), 1.69 (1H, dd, *J* 15.6 and 7.1 Hz, C*H*HCH($O_2$C)), 1.76 (3H, t(br), *J* ~1 Hz, C*H*$_3$C=CH$_2$), 2.15 (1H, dd, *J* 15.6 and 4.8 Hz, CH*H*CH($O_2$C)), 2.88 (1H, s(br), O*H*), 3.09 (1H, dd, *J* 13.6 and 9.5 Hz, C*H*HFur), 3.11–3.18 (1H, m(br), C*H*–C(Me)=CH$_2$), 3.33 (1H, dddd, *J* 8.8, 5.3, 1.8 and 1.2 Hz, CH=CHC*H*$CO_2$R), 3.35 (1H, dd, *J* 13.6 and 2.8 Hz, CH*H*Fur), 4.25 (1H, d(AB)q, *J* 11.0 and 7.1 Hz, $CO_2CH$*H*$CH_3$), 4.30 (1H, d(AB)q, *J* 11.0 and 7.1 Hz, $CO_2CH$*H*$CH_3$), 4.69–4.75 (1H, m(br), C*H*(OH)$CHO_2$C), 4.73 (1H, s(br), =C*H*H), 4.81 (1H, app. td, *J* 2 × ~7.1 and 4.8 Hz, CH(OH)C*H*$O_2$C), 4.88 (1H, d, *J* 0.4 Hz, FurC*H*(OR)), 4.89 (1H, app. quint, *J* 4 × ~1.5 Hz, =CH*H*), 5.25 (1H, ddd, *J* 16.2, 5.3 and 1.2 Hz, C*H*=CH), 5.90 (1H, ddd, *J* 16.2, 7.2 and 1.9 Hz, CH=C*H*), 6.66 (1H, s(br), Fur*H*); $\delta_C$ (100 MHz, $CDCl_3$) 14.3 ($CH_3$), 21.6 ($CH_3$), 25.9 ($CH_3$), 28.0 ($CH_3$), 28.9 ($CH_3$), 32.0 ($CH_2$), 38.9 ($CH_2$), 45.0 (CH), 49.8 (CH), 60.4 ($CH_2$), 69.9 (CH), 79.0 (CH), 81.8 (CH), 83.1 (C), 110.1 (C), 110.4 (C), 111.9 ($CH_2$), 115.4 (C), 123.1 (CH), 137.5 (CH), 145.3 (C), 150.1 (C), 160.8 (C), 163.4 (C), 174.8 (C); *m*/*z* (ESI) 483.1982 ($C_{25}H_{32}O_8Na^+$ requires 483.1989).
18. Data for diacetate **27**: $\delta_H$ (400 MHz, $CDCl_3$) 1.29 (1H, dd, *J* 15.6 and 10.3 Hz, C*H*HCH($O_2$C)), 1.34 (3H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.36 (3H, s, C*H*$_3$), 1.64 (1H, dd, *J* 15.6 and 3.7 Hz, CH*H*CH($O_2$C)), 1.76 (3H, s(br), C*H*$_3$C=CH$_2$), 2.20 (3H, s, C*H*$_3CO_2$), 2.22 (3H, s, C*H*$_3CO_2$), 2.89 (1H, dd, *J* 13.7 and 10.2 Hz, C*H*HFur), 3.11–3.17 (1H, m(br), C*H*–C(Me)=CH$_2$), 3.48 (1H, dd, *J* 13.7 and 4.4 Hz, CH*H*Fur), 3.60–3.65 (1H, m, CH=CHC*H*$CO_2$R), 4.25 (1H, d(AB)q, *J* 11.0 and 7.2 Hz, $CO_2CH$*H*$CH_3$), 4.30 (1H, d(AB)q, *J* 11.0 and 7.2 Hz, $CO_2CH$*H*$CH_3$), 4.77 (1H, s(br), =C*H*H), 4.91 (1H, app. quint, *J* 4 × ~1.5 Hz, =CH*H*), 5.05 (1H, ddd, *J* 10.3, 7.3 and 3.7 Hz, CH(OAc)C*H*$O_2$C), 5.31 (1H, ddd, *J* 16.2, 4.7 and 1.2 Hz, CH=C*H*$CHCO_2$), 5.43 (1H, dd, *J* 8.9 and 7.3 Hz, C*H*(OAc)$CHO_2$C), 5.67 (1H, s(br), FurC*H*OAc), 5.70 (1H, ddd, *J* 16.2, 7.3 and 2.2 Hz, C*H*=CHC$HCO_2$), 6.64 (1H, s(br), Fur*H*); $\delta_C$ (100 MHz, $CDCl_3$) 14.3 ($CH_3$), 20.6 ($CH_3$), 20.9 ($CH_3$), 21.7 ($CH_3$), 23.1 ($CH_3$), 31.7 ($CH_2$), 37.6 ($CH_2$), 42.9 (CH), 49.2 (CH), 60.4 ($CH_2$), 71.4 (CH), 73.6 (C), 74.5 (CH), 76.6 (CH), 110.0 (CH), 111.7 ($CH_2$), 115.4 (C), 122.9 (CH), 136.3 (CH), 145.5 (C), 148.8 (C), 159.9 (C), 163.3 (C), 169.7 (C), 170.2 (C), 172.4 (C); *m*/*z* (ESI) 527.1891 ($C_{26}H_{32}O_{10}Na^+$ requires 527.1888).