Tetrahedron Letters 51 (2010) 1280–1283

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of *exo* enol ether-cyclic ketal isomers of substituted furanmethanol structures related to marine furanocembranoids

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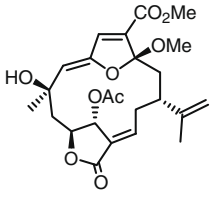
ARTICLE INFO

Article history:
Received 10 December 2009
Accepted 23 December 2009
Available online 7 January 2010

ABSTRACT

Oxidations of the 2-alkenylfurans **8a** and **8b**, using peroxy reagents, lead to the dienedione **9** and the furan epoxide **10**, respectively. Treatment of the epoxide **10** with *p*-TSA in MeOH produces the enol ether cyclic ketal **12**, which is rapidly isomerised to the furanmethanol ether **15**, isolated in 80% yield. By contrast, when the propanol-substituted furan epoxide **23** was kept in $CDCl_3$ containing traces of HCl for 2 h, a 3:2 mixture of *Z*- and *E*-isomers of the enol ether spiro ketals **25a** and **25b** was produced in >92% yield; after 24 h this mixture of isomers underwent dehydration leading to the corresponding enol ether triene **26** (70%). When a solution of the dienedione **9** in H_2O–THF containing *p*-TSA was stirred at 25 °C for 20 h, the tertiary alcohol **27** was produced which, after a further 20 h was converted into the furan vicinal diol **29**. Likewise, when the 'cembranoid' dienedione **31** was treated with *p*-TSA–H_2O, the hydroxymethyl-substituted furanobutenolide **33** was produced in 40% yield. It is probable that the enol ether cyclic hemiketals **28** and **32**/**34**, which are related to **12** and **25**, and also to the naturally occurring cembranoids **1** and **2** found in corals, are transient intermediates in the conversions leading to **29** and **33** from **9** and **31**, respectively.

exo Enol ether-cyclic ketal isomers of substituted furanmethanols are found in a small group of unusual secondary metabolites, for example, **1** and **2**, isolated from corals of the genus *Sinularia* and *Lophogorgia*.[1] The metabolites co-occur with substituted furanmethanol, furanoepoxide and *Z*-enedione-based diterpene 'cembranes', for example, **3**, **4** and **5**, to which they are probably interrelated biosynthetically.[2] It has also been suggested that *exo* enol ether-containing cembranoids are key intermediates in the



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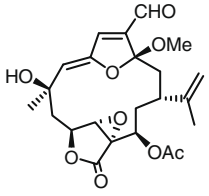

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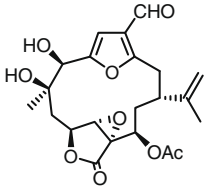

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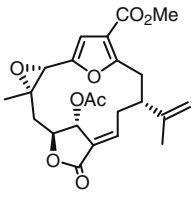

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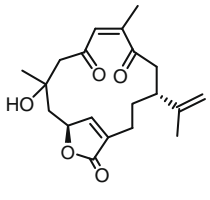

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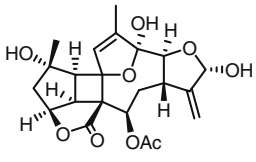

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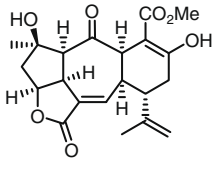

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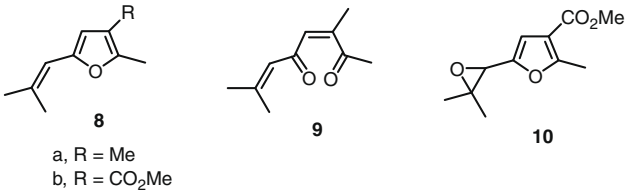
doi:10.1016/j.tetlet.2009.12.131

biosynthesis of more complex polycyclic diterpenes, for example, bielschowskysin **6** and rameswaralide **7**,[3] found in corals, involving novel transannular cycloaddition reactions.[4] To gain a closer insight into the likely origin of *exo* enol ether-cyclic ketal structures akin to **1** and **2**, we have investigated their synthesis from simple model furanoepoxide and enedione precursors related to **4** and **5**.

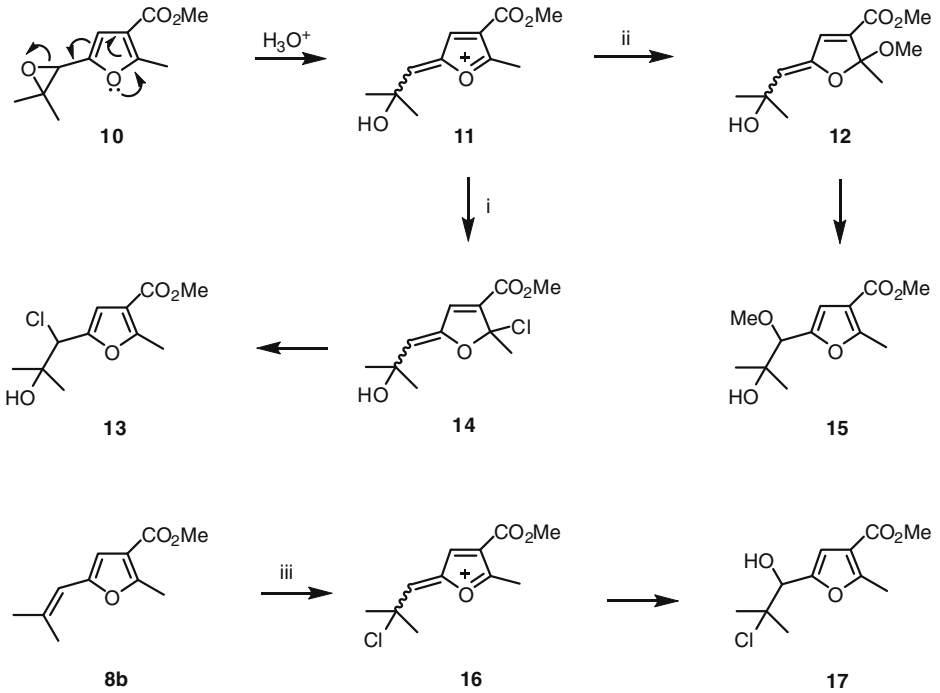
We first examined the oxidation/hydrolysis chemistry of the simple alkenyl furans **8a** and **8b**, which differ according to whether they have a Me or a CO_2Me group at C-3 in their furan rings. Thus, treatment of the C-3 methyl substituted alkenyl furan **8a** with peroxy reagents, that is, mCPBA, dimethyldioxirane (DMDO), Dess–Martin periodinane (DMP), resulted in specific oxidative cleavage of the furan ring, and formation of the *Z*-dienedione **9** in approx. 75% yield. By contrast, oxidation of the alkenylfuranoate **8b** using DMDO at −40 °C led to the corresponding epoxide **10** (84%). The variation in the pattern of oxidation of **8a** and **8b** reflects the deactivating effect of the CO_2Me group in the substrate **8b** towards oxidation of the furan ring relative to **8a**.[5,6]



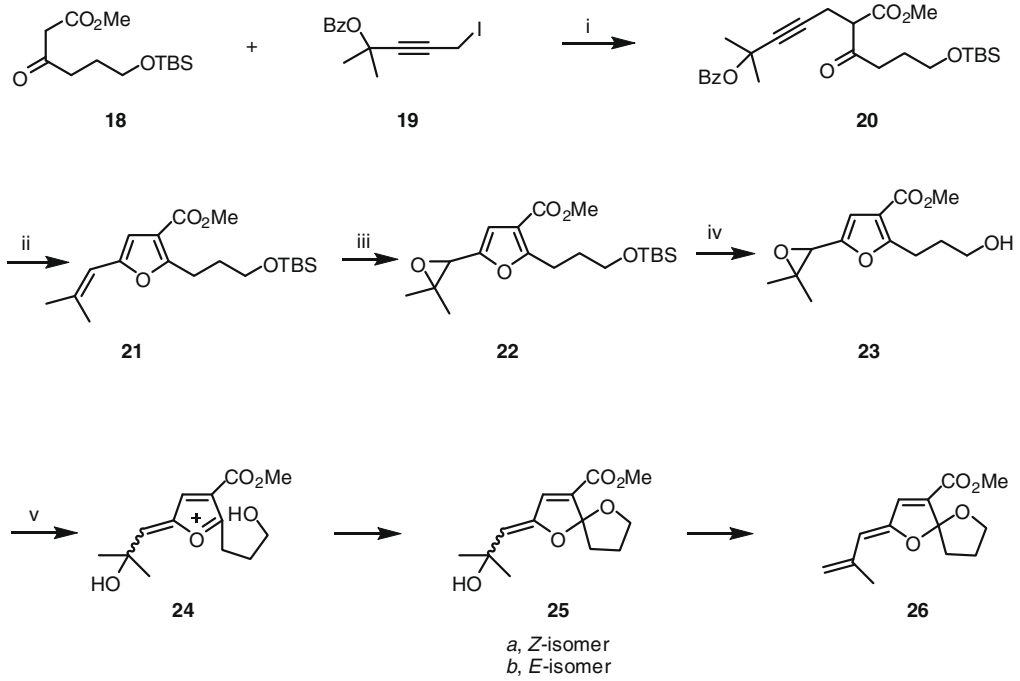
When a solution of the epoxide **10** in methanol was stirred in the presence of *p*-TSA at room temperature for 0.5 h, work-up and chromatography gave a single product corresponding to overall addition of methanol, in 80% yield. Comparison of pertinent NMR spectroscopic data recorded for the product, that is, δ^H 6.60 (s, =C*H*), 3.94 (s, C*H*OMe); δ^C 110.3 (d, =*C*H), 84.2 (d, *C*HOMe) ppm, with those reported for the natural products **1** and **2**, that is, δ^H 6.99 (s, =C*H*), 5.16 (s, OC=C*H*); δ^C 138.9 (d, =*C*H), 116.9 (d, OC=*C*H) ppm established unequivocally that it had the furanmethanol methyl ether structure **15**, and not the isomeric dihydrofuran enol ether structure **12** we might have anticipated.[7] When the same epoxide **10** was treated with aqueous HCl at room temperature overnight, the chlorohydrin **13** was isolated exclusively (65%), with no evidence for the presence of the isomeric enol ether structure **14** (Scheme 1). The structure of **13** followed unambiguously by comparison of NMR spectroscopic data with those of the isomeric chlorohydrin **17** produced from the alkenylfuran **8b** using aqueous *N*-chlorosuccinimide.[8]

It is likely that the products **13** and **15** are produced from the epoxide **10** via the same oxonium ion intermediate **11** and the enol ethers **12** and **14**, respectively, which are very rapidly isomerised under the reaction conditions to the more stable furan derivatives. Likewise, the chlorohydrin isomer **17** of **13** is derived from the alkenylfuran **8b** via the oxonium ion species **16** [cf. **11**], and possibly the isomeric enol ether [cf. **14**]. In each of the experiments carried out with the substrates **10** and **8b**, it is evident that the isomerisation of any enol ether intermediates, viz. **12** and **14**, to the corresponding furanmethanol derivatives **13** and **15**, respectively, is so rapid at ambient temperature, as to preclude their isolation and characterisation. Hence, in a more detailed study, a solution of epoxide **10** in $CDCl_3$ containing 10 equiv of methanol was treated with a crystal of *p*-TSA at room temperature and the reaction was monitored by ^{1}H NMR spectroscopy. After 5 min (30% conversion), the ^{1}H NMR spectrum demonstrated the formation of the *E*-isomer of the enol ether **12**, δ_H 5.37 (s, OC=C*H*), 7.87 (s, =C*H*), together with the isomeric furan structure **15** in the ratio 2:5. After a further 10 min (80% conversion) the ratio of **12** to **15** was 1:3.[9] Finally, after 25 min the only product observed by ^{1}H NMR spectroscopy was the furanmethanol methyl ether **15**.

In an effort to intercept and isolate an enol ether corresponding to **12**, we next studied the acid-catalysed hydrolysis of the



Scheme 1. Reagents and conditions: (i) aq HCl (2 M), rt overnight, 65%; (ii) MeOH, *p*-TSA (cat.), rt 0.5 h, 80%; (iii) NCS, H_2O, CH_2Cl_2, rt 2 d, 49%.

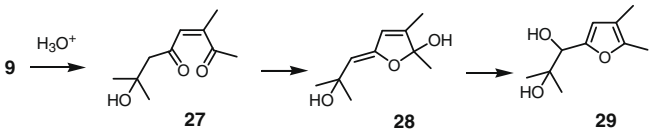


Scheme 2. Reagents and conditions: (i) NaH, THF, 0 °C, 72%; (ii) $Pd(OAc)_2$, dppf, K_2CO_3, CH_3CN/H_2O (10:1), rt 50%; (iii) DMDO, acetone, 0 °C, 78%; (iv) TBAF, THF, rt 71%; (v) HCl–$CDCl_3$, 70%.

substrate **23** which is substituted with a propanol group at C-2 in the furan ring. We anticipated that this propanol group might participate by quenching any oxonium ion species produced from **23**, that is, **24**, in an intramolecular fashion, thereby leading to an isolable enol ether. The substrate **23** was prepared by alkylation of the anion derived from the β-keto ester **18**,[10] with the propargyl iodide **19**,[11] followed by cyclisation of the resulting substituted β-keto ester **20** to the furan **21** using the conditions described by Wipf et al.[12] (Scheme 2). Epoxidation of the alkenylfuran **21** using DMDO next gave the epoxide **22** which was then deprotected using TBAF, leading to the desired propanol-substituted furan epoxide **23**.

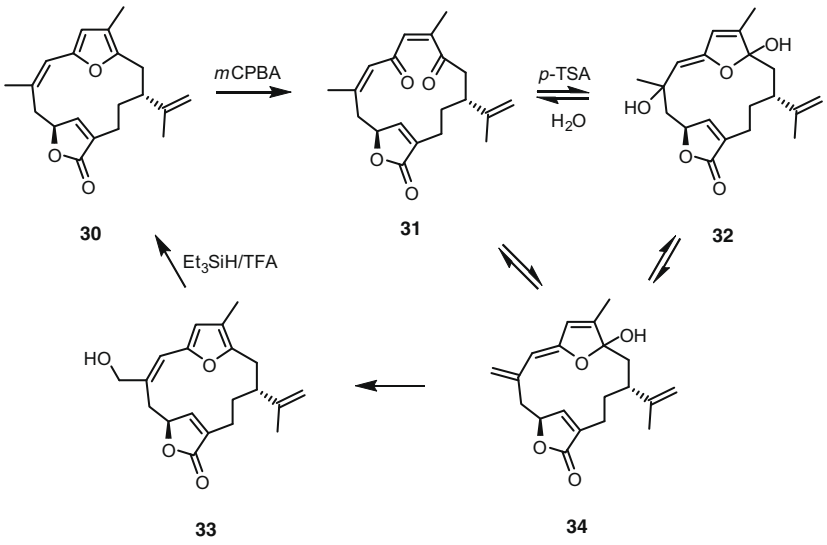
When a solution of the epoxide **23** in $CDCl_3$ (containing traces of HCl) was left at room temperature for 0.5 h, ^{1}H NMR spectroscopic analysis showed that it was converted (30%) into a 4:3 mixture of *Z*-[δ_H 5.00 (OC=C*H*), 6.92 (=C*H*)], and *E*-[δ_H 5.35 (OC=C*H*), 7.83 (=C*H*)] isomers of the *exo* enol ether spiroketal structures **25a** and **25b**, respectively.[13] After 2 h, the conversion of **23** into **25a** and **25b** (ratio 3:2) was essentially complete (>92%),[14] and when the solution was left for a further 24 h, the only product isolated, in 70% yield, was a single isomer of enol ether triene **26**, resulting from dehydration of **24**/**25**.[15] The *Z*-stereochemistry assigned to **26** followed from a NOESY correlation analysis.

In a separate study, a solution of the *Z*-dienedione **9** in H_2O–THF containing *p*-TSA was stirred at room temperature and the progress of the reaction was monitored by ^{1}H NMR spectroscopy. After ca. 20 h, work-up and chromatography gave the tertiary alcohol **27** (10%), resulting from hydration of the terminal alkene bond in **9,** as the first-formed product.[16] When the reaction of **9** with *p*-TSA in H_2O–THF was left longer, or when the hydroxyenedione **27** was treated again with *p*-TSA–H_2O–THF for ca. 20 h, the only product isolated was the furan vicinal diol structure **29**.[16] As with the epoxide **10**, we believe that the enol ether **28** is a likely intermediate in the conversion of **9** and **27** into **29**, but the isomerisation of **28** into **29** is too rapid under the reaction conditions to allow its separate isolation.



Finally, we examined the acid-catalysed isomerisation of a *Z*-dienedione contained within a macrocyclic cembranoid, that is, **31**, with the expectation that this substrate would be 'locked' conformationally, thereby favouring the formation of an isolable enol ether-cyclic hemiketal, that is, **32**. Thus, oxidative cleavage of the furan ring in the furanobutenolide **30** (rubifolide)**,** first gave the enedione **31** (also known as isoepilophodione B).[17] When the enedione **31** was treated with *p*-TSA–H_2O, a single product was isolated in 40% yield, whose spectroscopic data were consistent with the hydroxymethyl-substituted alkenylfuran structure **33**[18] and not with the structure **32**. Indeed, reduction of the alcohol group in the product, using Et_3SiH–TFA in CH_2Cl_2 at 0 °C, regenerated rubifolide **30** in 56% yield. We rationalise the formation of **33** from **31**, taking place by acid-catalysed hydration–enolisation of **31** via the enol ether intermediates **32** and **34**, followed by isomerisation of **34** to the corresponding alkenylfuran **33**. Once again, therefore, our efforts to interrupt the rapid isomerisation of enol ether-cyclic hemiketals to their furan counterparts, and to isolate cembranoid compounds, viz. **32**, similar in constitution to natural products, that is, **1** and **2**, were thwarted.

In conclusion, the enol ether cyclic ketals **12** and **25**, having structural features in common with the novel cembranoid natural products **1** and **2**, have been synthesised and characterised. Similar enol ethers have been implicated in the conversions of the epoxide **10**, the 2-alkenylfuran **8b**, and the dienediones **9** and **31** into the substituted furans **13**, **17**, **29** and **33**, respectively. However, further studies, involving subtle changes to the structures of precursors are required before a clearer insight into the origin of cembranoid enol ether cyclic ketals and their importance in biosynthetic pathways is to be forthcoming. These investigations are in progress in our laboratory.



Acknowledgements

We thank the EPSRC for a Fellowship (to Y.L.) and for a Studentship (to J.R.). We also thank Merck for support, and Bencan Tang and Amael Veyron for some initial studies in this area.

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7. The furanmethanol methyl ether **15** showed: δ_H (400 MHz, $CDCl_3$): 6.60 (1H, s, =C*H*), 3.94 (1H, s, C*H*(OMe)), 3.83 (3H, s, C(O)O*Me*), 3.32 (3H, s, (*Me*O)CH), 3.28 (1H, s, MeMeC(O*H*)), 2.59 (3H, s, =C*Me*), 1.22 (3H, s, *Me*MeC(OH)), 1.21 (3H, s, Me*Me*C(OH)); δ_C (100 MHz, $CDCl_3$): 164.5 (s), 159.3 (s), 149.8 (s), 113.8 (s), 110.3 (d), 84.2 (d), 72.5 (s), 57.6 (q), 51.3 (q), 25.9 (q), 24.5 (q), 13.9 (q); HRMS (ESI) 265.1043 ($M+Na^+$, $C_{12}H_{18}O_5Na$ requires 265.1052).
8. The chlorohydrin **13** showed: δ_H (400 MHz, $CDCl_3$): 6.69 (1H, s, =C*H*), 4.86 (1H, s, C*H*(Cl)C), 3.84 (3H, s, C(O)O*Me*), 2.61 (3H, s, *Me*C=), 2.29 (1H, br s, MeMeC(O*H*)),1.39 (3H, s, *Me*MeCH(OH)), 1.37 (3H, s, Me*Me*CH(OH)); δ_C (100 MHz, $CDCl_3$): 164.1 (s), 159.5 (s), 149.0 (s), 114.2 (s), 110.7 (d), 73.0 (s), 64.9 (d), 51.5 (q), 26.9 (q), 25.8 (q), 13.9 (q). The isomeric chlorohydrin **17** showed: δ_H (400 MHz, $CDCl_3$): 6.63 (1H, s, =C*H*), 4.64 (1H, d, *J* 5.2, C*H*(OH)C), 3.81 (3H, s, CO_2*Me*), 2.65 (1H, d, *J* 5.2, CH(O*H*)C), 2.57 (3H, s, *Me*C=), 1.67 (3H, s, *Me*MeCH(Cl)), 1.65 (3H, s, Me*Me*CH(Cl)); δ_C (100 MHz, $CDCl_3$): 164.3 (s), 158.9 (s), 150.1 (s), 113.9 (s), 109.5 (d), 75.5 (d), 73.8 (s), 51.4 (q), 29.5 (q), 27.1 (q), 13.8 (q); HRMS (ESI) 269.0517 ($M+Na^+$, $C_{11}H_{15}ClO_4Na$ requires 269.0557).
9. The enol ether cyclic ketal **12** showed: δ_H (400 MHz, $CDCl_3$): 7.87 (1H, s, =C*H*), 5.37 (1H, s, OC=C*H*), 3.81 (3H, s, CO_2*Me*), 3.14 (3H, s, O*Me*), 2.58 (3H, s, MeOC*Me*), 1.70 (3H, s, C*Me*Me), 1.42 (3H, s, CMe*Me*).
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14. The *Z*-enol ether **25a** showed: δ_H (400 MHz, $CDCl_3$): 6.92 (1H, s, =C*H*), 5.0 (1H, s, OC=C*H*), 4.21–4.03 (2H, m, OCH_2), 3.81 (3H, s, O*Me*), 2.65–2.56 (1H, m, OCH_2C*H*H), 2.25–2.10 (3H, m, OCH_2CHHCH_2), 1.44 (3H, s, C*Me*Me), 1.42 (3H, s, CMe*Me*); The *E*-enol ether **25b** showed: δ_H (400 MHz, $CDCl_3$): 7.83 (1H, d, *J* 0.4, =C*H*), 5.35 (1H, d, *J* 0.4, OC=C*H*), 4.21–4.03 (2H, m, OCH_2), 3.81 (3H, s, O*Me*), 2.65–2.56 (1H, m, OCH_2C*H*H), 2.25–2.10 (3H, m, OCH_2CHHCH_2), 1.44 (3H, s, C*Me*Me), 1.42 (3H, s, CMe*Me*); HRMS (ESI) 277.1043 ($M+Na^+$, $C_{13}H_{18}O_5Na$ requires 277.1052).
15. The *Z*-enol ether triene **26** showed: δ_H (400 MHz, $CDCl_3$): 6.96 (1H, s, =C*H*), 5.31 (1H, s, OC=C*H*), 5.18 (1H, br s, =CH*H*), 4.97 (1H, br s, =CH*H*), 4.18 (1H, app. dt, *J* 7.5 and 4.5, OC*H*H), 4.08 (1H, app. q, *J* 7.4, OCH*H*), 3.81 (3H, s, O*Me*), 2.63–2.53 (1H, m, OCH_2C*H*H), 2.30–2.12 (3H, m, OCH_2CHHCH_2), 2.15 (3H, s, =C*Me*); δ_C (100 MHz, $CDCl_3$): 168.2 (s), 157.9 (s), 153.1 (s), 140.3 (s), 138.1 (d), 132.2 (s), 117.0 (t), 109.8 (d), 69.8 (t), 51.7 (q), 35.1 (t), 25.1 (t), 22.4 (q); HRMS (ESI) 237.1119 ($M+H^+$, $C_{13}H_{17}O_4$ requires 237.1127).
16. The β-hydroxyketone **27** showed: ν_{max} (film)/cm^{-1} 3642, 3516, 1704, 1614; δ_H (400 MHz, $CDCl_3$): 6.03 (1H, q, *J* 1.5, =C*H*), 3.53 (1H, br s, Me_2C*O*H), 2.67 (2H, s, CH_2), 2.32 (3H, s, CO*Me*), 2.00 (3H, d, *J* 1.5, =C*Me*), 1.27 (6H, s, Me_2COH); δ_C (100 MHz, $CDCl_3$): 206.6 (s), 200.2 (s), 156.7 (s), 124.6 (d), 69.8 (s), 53.3 (t), 29.4 (2 × q), 28.0 (q), 20.3 (q); HRMS (ESI) 207.0989 ($M+Na^+$, $C_{10}H_{16}O_3Na$ requires 207.0992). The furan vicinal diol **29** showed ν_{max} ($CHCl_3$ solution)/cm^{-1} 3578, 2927, 1704, 1672; δ_H (300 MHz, $CDCl_3$): 6.08 (1H, s, =C*H*), 4.38 (1H, br s, C*H*(OH)C), 2.19 (3H, s, =C*Me*), 1.92 (3H, s, =C*Me*), 1.28 (3H, s, *Me*MeC), 1.26 (2H, br s, 2 × O*H*), 1.19 (3H, s, Me*Me*C); δ_C (75 MHz, $CDCl_3$): 150.7 (s), 147.0 (s), 114.5 (s), 111.3 (d), 74.7 (q), 73.1 (s), 26.0 (q), 25.0 (q), 11.4 (q), 9.8 (q); HRMS (ESI) 207.0988 ($M+Na^+$, $C_{10}H_{16}O_3Na$ requires 207.0992). For a special example of the transition of a cyclic bis-ketal enedione to an *exo* enol ether-cyclic ketal, where the enol ether is part of a vinylogous carbonate, see: Etchells, L. L.; Sardarian, A.; Whitehead, R. C. *Tetrahedron Lett.* **2005**, *46*, 2803–2807.
17. Roethle, P. A.; Hernandez, P. T.; Trauner, D. *Org. Lett.* **2006**, *8*, 5901–5904.
18. The 19-hydroxyrubifolide **33** showed: ν_{max} ($CHCl_3$ solution)/cm^{-1} 3452, 1748, 1646, 1628; δ_H (400 MHz, $CDCl_3$) (cembrane ring numbering): 6.90 (1H, app. t, *J* 1.5, H-11), 6.33 (1H, br s, H-7), 6.14 (1H, br s, H-5), 5.10–5.03 (1H, m, H-10), 4.94–4.87 (2H, m, H-16), 4.29 (2H, app. d, *J* ~3.0, H-19), 3.17 (1H, app. t, *J* ~12, H-9β), 2.87 (1H, dd, *J* 12.1 and 4.4, H-9α), 2.64–2.33 (4H, m, H-2, H-1 and H-13β), 2.14–2.05 (1H, m, H-13α), 1.94 (3H, br s, H-18), 1.75 (3H, br s, H-17), 1.70–1.58 (2H, m, H-14β and CH_2O*H*), 1.17 (1H, ddt, *J* 13.8, 3.3 and 0.8, H-14α); δ_C (100 MHz, $CDCl_3$): 174.5 (s), 151.9 (d), 150.6 (s), 149.3 (s), 145.4 (s), 132.9 (s), 129.1 (s), 117.6 (s), 117.6 (d), 116.0 (d), 113.1 (t), 79.6 (d), 68.3 (t), 43.4 (d), 35.9 (t). 31.2 (t), 30.6 (t), 20.1 (t), 19.2 (q), 9.6 (q); HRMS (ESI) 351.1566 ($M+Na^+$, $C_{20}H_{24}O_4Na$ requires 351.1567).