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Insight into Pyridinium Chlorochromate Chemistry: Catalytic Oxidation of Tetrahydrofuran Compounds and Synthesis of Umbelactone

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The catalytic system PCC (cat.)/H_5IO_6 has been used to oxidise mono- and polytetrahydrofuran compounds. New oxidative pathways are disclosed. 2,2,5-Trisubstituted THF rings are converted into dicarbonyl compounds through oxidative cleavage of the C2–C3 bond. Cyclic enol ethers appear to be intermediate species in this process. Oxidation of 2,2,5-trisubstituted α-keto-THF compounds proceeds with the oxidative cleavage of the C2(THF)–C=O bond to give 1,4-diketones with degraded carbon backbones. Attack of the oxidant on 2,5-disubstituted THF rings leads to 1,4-diketones containing intact THF carbon frameworks. Oxidation of complex poly-THF substrates, containing up to five THF rings, allows access to new poly-THF compounds through regioselective THF oxidation along the poly-THF backbones. A mechanistic explanation of the new processes consistent with the reported reactivity of PCC and the isolation of some minor products of the process is provided. The synthesis of racemic umbelactone, an antiviral natural butenolide metabolite, has been carried out by use of the developed chemistry.

Introduction

Pyridinium chlorochromate (PCC) is a well-known reagent employed in an array of oxidising processes.[1] This oxidant is usually used either in stoichiometric or in excess amounts to oxidise a variety of functional groups. In contrast, the use of PCC in catalytic amounts has received little attention to date[2,3] even though chromium(VI) species are known to be carcinogenic and environmentally hazardous and the use of substoichiometric amounts of such a reagent would therefore be highly desirable. In this respect, the catalytic system PCC (cat.)/H_5IO_6 is particularly appealing, although it has been employed in only a few cases.[2,3] As a part of our ongoing interest in oxidative processes mediated by transition metal oxo species[4] and in particular in the synthesis of new THF-containing compounds,[5] we report here on the oxidation of mono- and poly-THF compounds with the PCC (cat.)/H_5IO_6 (chlorochromatoperiodate, CCP) system, which has led to the discovery of new types of useful oxidative transformations involving THF ring systems. A similarity between the oxidative behaviour of PCC and that of RuO_4, which further supported our recent findings in the chemistry of these oxo species, has also emerged.[5a,5b]

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Results and Discussion

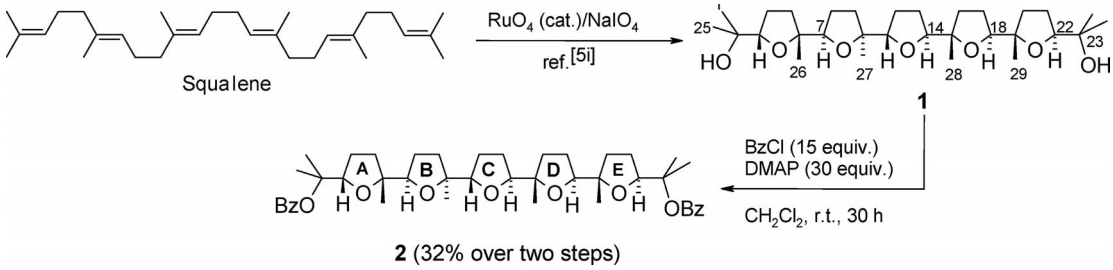
Oxidation of Poly-THF Compounds – Preliminary Results

In a preliminary experiment devised to test the reactivities of tetrahydrofuran-containing substances with PCC, penta-THF dibenzoate **2** (Scheme 1), containing five differently substituted and configured THF rings, was investigated. The synthesis of **2** was accomplished by a RuO_4-catalysed oxidative polycyclization protocol starting from squalene, previously developed in our laboratory,[5i,5f] followed by benzoylation of the tertiary hydroxy groups in the initially formed penta-THF diol **1** under standard conditions (BzCl, DMAP, CH_2Cl_2).

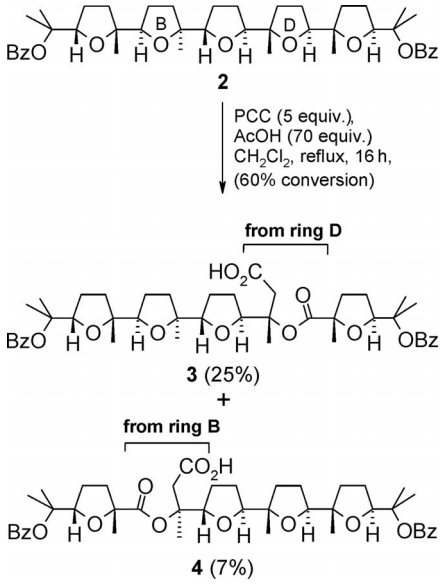
Treatment of **2** with PCC under classical oxidising conditions (excess PCC/AcOH, CH_2Cl_2, Scheme 2)[5b] gave the two isomeric tetra-THF compounds **3** and **4** (overall 32% yield), originating from the oxidative cleavage of the C2–C3 bonds in either the D or the B THF rings of **2**, respectively.

The rest of the material for mass balance was made up of polar substances possibly derived by side- or over-oxidation processes due to the presence of various THF rings prone to attack by the oxidant. The structures of **3** and **4** were determined by a full set of 2D NMR experiments recorded at high fields. Although the process proceeded with a rather low yield and could not be forced to completion under these conditions, the ability of PCC to oxidise the THF ring had been confirmed.

Our next goal was to test the reactivity of **2** in the presence of the catalytic system PCC (cat.)/H_5IO_6 (Scheme 3). From previous studies[6] it is thought that the combination of PCC and H_5IO_6 generates chlorochromatoperiodate

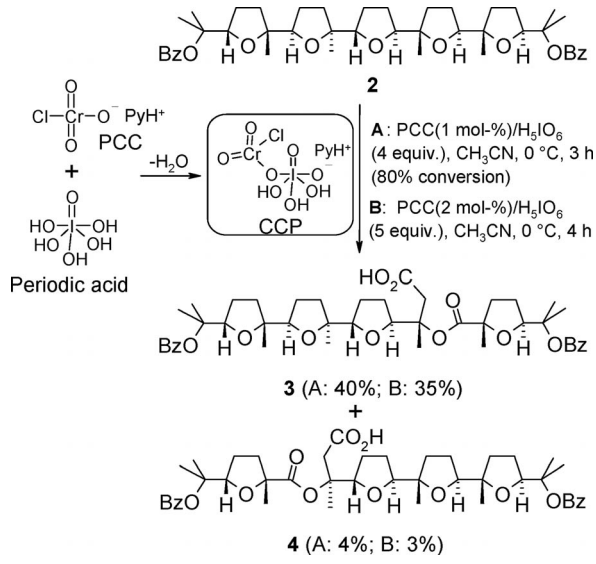


Scheme 1. Synthesis of penta-THF dibenzoate **2**.



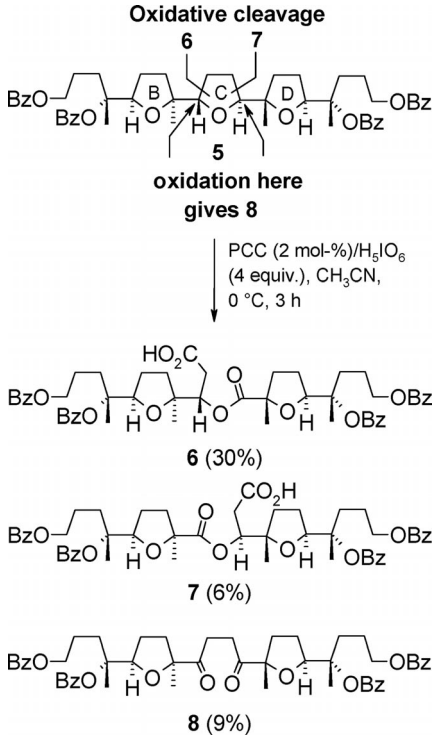
Scheme 2. Cleavage products from the oxidation of penta-THF dibenzoate **2** with PCC/AcOH.

(CCP, Scheme 3), an oxidising agent more powerful than PCC itself. It was hoped that the use of a more reactive reagent such as this might possibly reduce reaction times and force the process to completion. The oxidation was initially carried out in CH_3CN at 0 °C with 1 mol-% of PCC and 4 equiv. of periodic acid (Scheme 3, conditions A). The process was indeed much cleaner under these conditions and overall improved yields of acids **3** and **4** (**3**: 40%; **4**: 4%) were obtained in a shorter time (3 h). Importantly, the two isomers were now obtained in a ca. 10:1 ratio in favour of **3**. With regard to the attack of the oxidant at the D ring of the poly-THF system of **2**, the observed enhanced regioselectivity was probably due both to the increased steric demand of the CCP and to the different configurations of the involved rings (ring B: *cis*; ring D: *trans*). Under these conditions the process was still incomplete and stopped at 80% conversion. Addition of a further 1 mol-% PCC and 1 equiv. of H_5IO_6 (conditions B) forced the process to completion at the expense of a slight reduction in the overall yield (**3** + **4** 38%; **3**/**4** 10:1) presumably due to the over-oxidation of **3** and **4** themselves, as indicated by the presence of polar products, probably related to **3** and/or **4**, in the reaction mixture (NMR, HPLC and MS analyses). Smaller amounts of these side products were also formed under conditions A.



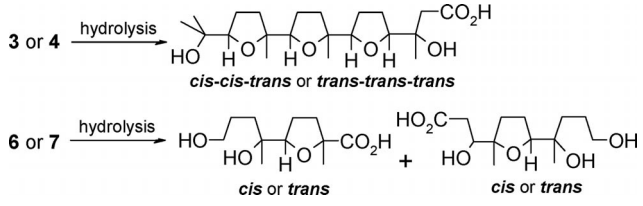
Scheme 3. Oxidation of penta-THF dibenzoate **2** with PCC (cat.)/H_5IO_6.

To test the above oxidising system further, the oxidation of tris-THF tetrabenzoate **5** (Scheme 4), a structurally "simplified" substrate related to **2**, was then carried out. Compound **5** was obtained by benzoylation of the corresponding tetrol (prepared in turn from penta-THF **1** through a short degradative sequence developed in a previous study conducted by our group[5f]). Interestingly, in this case the three major products **6**–**8**, two of them – acids **6** and **7** – structurally related to **3** and **4** and all originating from attack of the oxidant at the central THF ring, were obtained. In this case 4 equiv. of H_5IO_6 were sufficient to drive the process to completion. 2D NMR experiments were carried out to determine the stereostructures of **6**–**8**. A new feature of this process was the formation of the 1,4-diketone **8** through a different oxidative route featuring the oxidation of both the angular carbons of the central THF ring in **5**, not observed in the oxidation of penta-THF **2**. 1,4-Diketones are easily transformed into five-membered heterocycles, so substances such as **8** might be synthetically useful to access new types of rare mixed poly-THF/heterocycle compounds.



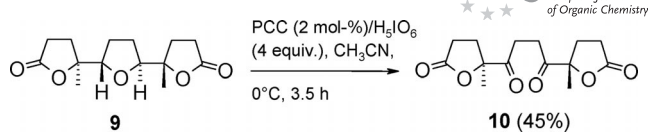
Scheme 4. Oxidation of tris-THF tetrabenzoate **5**.

The parent penta-THF **2** can be obtained in a single step in multi-gram amounts from cheap and commercially available squalene, so the oxidative degradation of its penta-THF backbone can allow facile access to stereochemically definite and functionalised *cis-cis-trans* and *trans-trans-trans* tris-THF compounds by hydrolysis of the inter-THF ester functions in either **3** or **4** (Scheme 5). Likewise, new functionalised *cis* or *trans* mono-THF systems can be obtained from **6** and **7** by hydrolysis (Scheme 5). Given literature precedents, it can be presumed that at least some of these substances should be useful for further cytotoxic activity studies and also for synthetic purposes.[7]



Scheme 5. Functionalised new all-*threo* mono- and tris-THF systems accessible through hydrolysis of poly-THF compounds **3**, **4**, **6** and **7**.

A further simplification of the poly-THF substrate was achieved by conversion of the tetrol corresponding to **5** into bis-lactone **9** (Scheme 6) through a previously developed degradative sequence.[5f] Interestingly, oxidation of this compound under the same conditions as used for **5** led to 1,4-diketone **10** (45% yield) through the oxidative opening of the THF ring, whereas no acid corresponding to compounds **6/7** was observed.



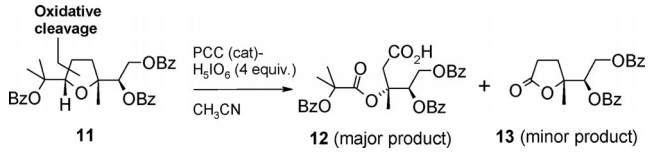
Scheme 6. Oxidation of THF-dilactone **9**.

The above results indicated that the oxidation of complex poly-THF compounds containing both di- and trisubstituted THF rings proceeds through two main routes. Oxidative cleavage of the C2–C3 bond is preferred when a 2,2,5-trisubstituted THF ring is involved, as in the oxidation of **2**. A second route leads to 1,4-diketones, such as **8** and **10**, through the attack of the oxidant at a 2,5-disubstituted THF ring and oxidation of both its angular carbon atoms, as in the oxidations of **5** and **9**.

Oxidation of Mono-THF Compounds

With the aim of making the above process synthetically useful, the oxidation of some mono-THF compounds, based on the di- and trisubstituted THF motifs present in previously studied poly-THF compounds, was tested. *cis*-THF **11** (Table 1), obtained by benzoylation of the corresponding diol, in turn synthesized by RuO_4-catalyzed oxidative cyclization of geranyl benzoate,[8] was initially chosen as a model compound to find the best conditions for the oxidative process. Oxidation of **11** under previously employed conditions [PCC (2 mol-%), H_5IO_6 (4 equiv.), 0 °C] gave acid **12**, analogous to compounds **3/4** and **6/7** obtained from more complex substrates, in a 54% yield (Table 1, Entry 1), although longer reaction times were required. The process was then carried out at room temp. with the same amounts of catalysts and co-oxidant, leading to **12** in a similar 55% yield in only 3 h (Entry 2). Improved yields (80%) and further reduced reaction times (45 min) were achieved by increasing the catalyst amount to 5% (Entry 3). Increasing of the catalyst amount to 10% resulted in a similar yield and further reduced times (78%, 30 min, Entry 4). Further increasing of the catalyst up to stoichiometric amounts (50–

Table 1. Optimization of the process on a model 2,2,5-trisubstituted THF compound.

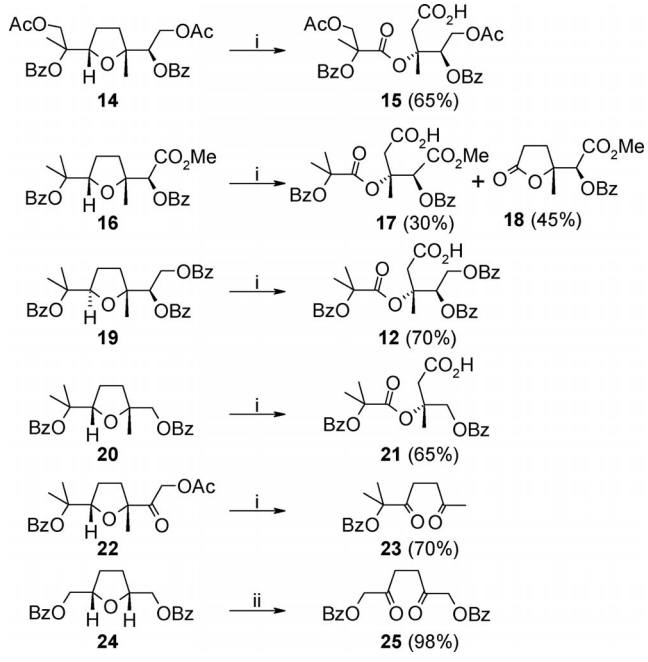


Entry	PCC [mol-%]	H_5IO_6 [equiv.]	Time	Yield of **12**[a] [%]
1[b]	2	4	19 h	54
2	2	4	3 h	55
3	**5**	**4**	**45 min**	**80**[c]
4	10	4	30 min	78
5	50	4	30 min	62
6	100	4	30 min	37

[a] Estimated by ^1H NMR examination of the crude mixture. [b] Carried out at 0 °C. [c] Isolated yield.

100%) only resulted in diminished yields (Entries 5 and 6). Finally, the effect of addition of water to the process was tested. Although the related system CrO_3(cat.)/H_5IO_6 has been successfully used to oxidise alcohols cleanly in wet CH_3CN (0.75 vol.-% water)[9] in our case we have observed that addition of water (2–5 vol.-%) is detrimental, causing the process to stop at 10–20% conversion.

Oxidation of mono-THF compounds structurally related to **11** under the optimized conditions was then carried out (Scheme 7). *cis*-THF compounds **14**, **16** and **24** were synthesized by benzoylation of the corresponding THF diols, in turn obtained by RuO_4-catalysed oxidative cyclization of *trans*,*trans*-2,6-dimethyl-2,6-octadiene-1,8-diol diacetate,[5j] methyl geranate[5j] and hexa-1,5-diene,[8] respectively, as reported. *trans*-THF **19** was obtained by benzoylation of the corresponding THF diol, a minor product from the oxidative cyclization of geranyl benzoate.[10] THF **20** was synthesized from **11** through a short sequence. In particular, selective removal of both the primary and secondary benzoates in **11** with K_2CO_3 in MeOH proceeded cleanly to give the corresponding diol. Oxidative cleavage of the diol system by treatment with silica-supported $NaIO_4$[11] in CH_2Cl_2, followed by borohydride reduction and benzoylation, afforded dibenzoate **20** in 43% yield (over four steps). Ketone **22** was obtained by TPAP-catalysed oxidative cyclization of geranyl acetate[5g] followed by benzoylation.



Scheme 7. Oxidation of functionalised 2,5-disubstituted and 2,2,5-trisubstituted THF compounds. i) PCC (5 mol-%), H_5IO_6 (4 equiv.), CH_3CN, room temp., 1 h; ii) PCC (2 mol-%), H_5IO_6 (4 equiv.), CH_3CN, room temp., 40 min.

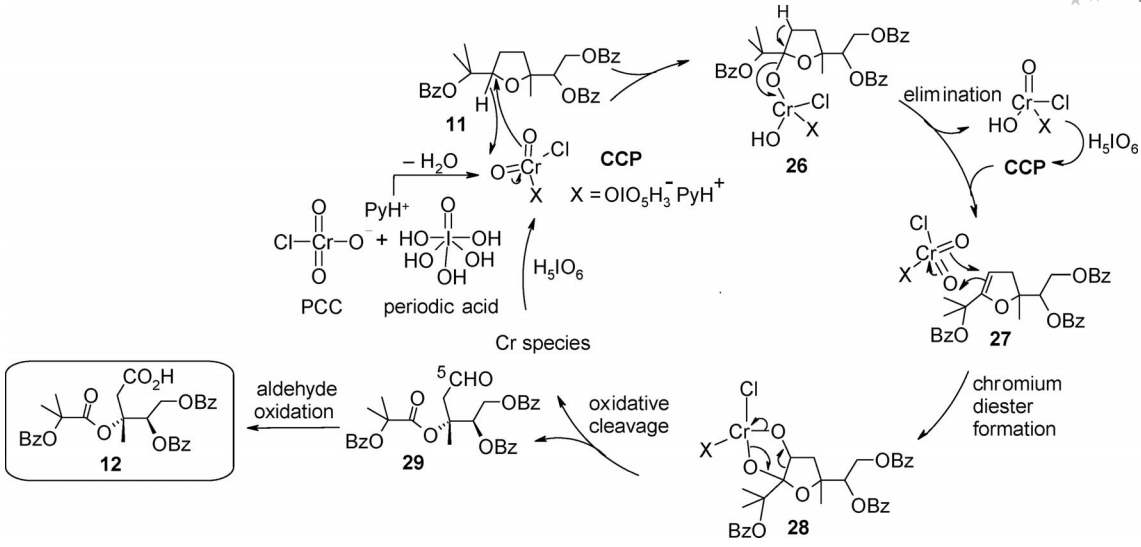
CCP oxidation of *cis*-THF diacetate **14** and *trans*-THF **19** gave acids **15** and **12**, respectively, in 65–70% yields. The methoxycarbonyl derivative **16** unexpectedly afforded the corresponding acid in a diminished 30% yield, the major product of the process being lactone **18**, analogous to **13**, derived from the oxidative removal of the dimethylated left-hand side chain. This side process is unusual but is reminiscent of the oxidative cleavage of a similar substrate.[3] This type of lactone is also the main side product of the process carried out on all the other substrates. Similarly, the THF derivative **20** gave acid **21** in 65% yield.

In another experiment, α-keto THF **22** was oxidised. In this case the presence of a keto group adjacent to the THF ring induced removal of the side chain through the oxidative cleavage of the C(THF)2–C=O bond to give 1,4-diketone **23** in good yields.

Finally, the reactivity of the 2,5-disubstituted *cis*-mono-THF **24** was tested. Pleasingly, 1,4-diketone **25** was obtained in a nearly quantitative yield (98%) even when the amount of PCC was reduced to 2 mol-%, This process is particularly appealing because it allows, when coupled with the oxidative cyclization of 1,5-dienes, the transformation of the latter into bis-ketols in a regioselective manner. This experiment and the oxidation of the more complex disubstituted mono-THF **9** demonstrated that for substrates containing only a 2,5-disubstituted THF ring the preferred route is the one leading to 1,4-diketones.

Isolation of Minor Products and Mechanistic Considerations

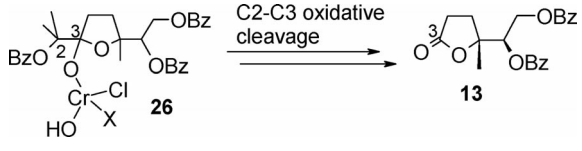
A plausible mechanistic route based on the known reactivity of PCC and related oxo species such as RuO_4[5a] was hypothesised to explain the formation of the above compounds. In particular, a pathway leading to compound **12** is shown in Scheme 8, but it also applies to the formation of the analogous compounds **3/4**, **6/7**, **15**, **17** and **21**. It is likely that the process begins with the attack of CCP, formed by elimination of water from PCC and periodic acid, at the angular C–H bond of the THF ring to give the mixed chromium ester intermediate **26**. This step is conceivably a [3+2] addition of the O=Cr=O portion of the oxidant to the angular C–H bond of the THF ring, as also hypothesised for the RuO_4 oxidation of neoisocedrane oxide,[12] a sesquiterpene containing a THF ring. It is reported that the oxidation of the THF ring in this substance proceeds through the intramolecular insertion of an oxoruthenium bond into the angular C–H bond of the THF ring. In addition, it has been suggested that attack of transition metal oxo species such as OsO_4 and RuO_4 to C–H bonds of alkanes also proceeds through a [3+2] addition of a C–H bond across an O=M=O unit,[13] through a mechanism analogous to the one now widely accepted for alkene bishydroxylation. In the next step, chromium ester **26** would give rise to cyclic enol ether **27** through an elimination step delivering a low-valent chromium species that would then be reoxidised to CCP by H_5IO_6. However, it cannot be excluded that the first step of the process could proceed through hydride abstraction from the angular C–H bond (not shown) by the same O=Cr=O portion of CCP to give an intermediate carbocation (actually an oxonium ion) which could then collapse to form enol ether **27**. This would



Scheme 8. A plausible catalytic cycle explaining the formation of acid **12**.

be consistent with the mechanism proposed by Lee and van den Engh for the RuO_4 oxidation of tetrahydrofuran to γ-butyrolactone,[14] in which the initially formed carbonium ion and Ru^{VI} oxo species recombine to give an intermediate ester similar to **26**.

Whereas PCC is unable to cleave isolated (unactivated) carbon-carbon double bonds, oxidative cleavages of both cyclic and acyclic enol ethers to esters with PCC have been reported.[15] In particular, the conversion of **27** to the final dicarbonyl compound **12** is thought to proceed through the formation of the chromium diester intermediate **28**, by a second [3+2] addition step. Oxidative cleavage to afford aldehyde **29**, followed by oxidation, eventually generates acid **12**. The conversion of **27** to **29** agrees well with the previously observed oxidative cleavage of cyclic enol ethers lacking α-hydrogen atoms.[15a,15c] Finally, formation of lactone **13**, the main side-product of the oxidation of **11** (Table 1), can be seen to originate from the oxidative removal of the dimethyl benzoate side chain. It has previously been observed that THF rings bearing a tertiary (free) alcohol functions undergo similar oxidative cleavage with CCP to give γ-lactones[3] such as **13**, via C-2 chromium ester intermediates. It is conceivable that a similar route could be responsible for the C2–C3 oxidative cleavage in a chromium ester intermediate possibly formed by further evolution of **26** (Scheme 9). This interaction is supported by the complete absence of hydrolysis of the primary and secondary benzoate functions present in the same molecule.



Scheme 9. Formation of lactone **13** by side-chain removal in intermediate **26**.

To support the mechanistic path shown in Scheme 8, a careful examination of the minor products formed during the oxidation of penta-THF **2**, both with PCC/AcOH and with CCP, was undertaken. HPLC analyses (direct and reversed-phase modes) led to the identification of the three side-products **30**–**32** (Figure 1) in both processes. Their structures give strong support for the proposed mechanism and their formation could be interpreted through routes consistent with those given for the main oxidation products.

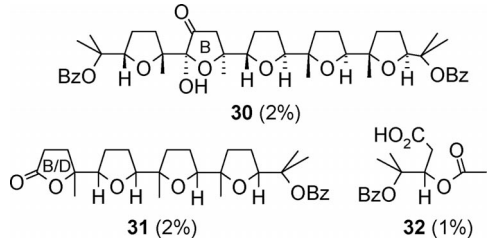
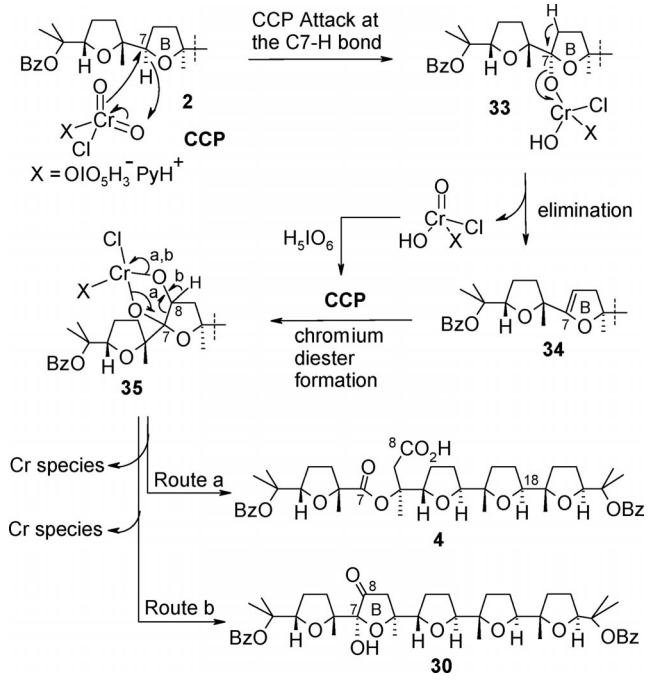
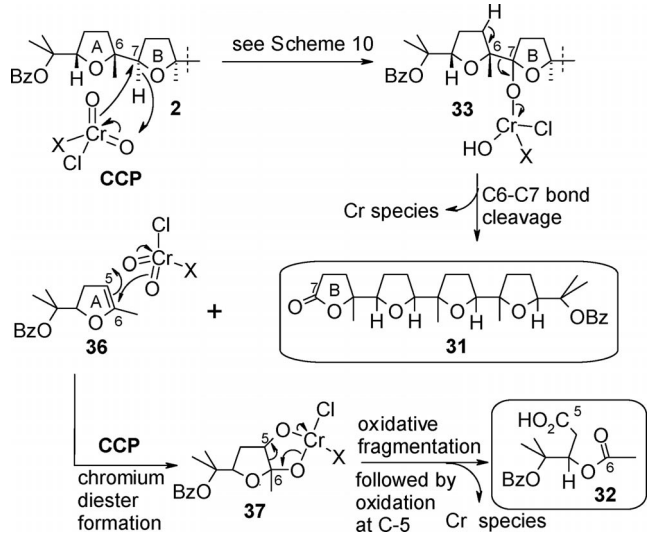


Figure 1. Minor products obtained from the oxidation of penta-THF dibenzoate **2**.

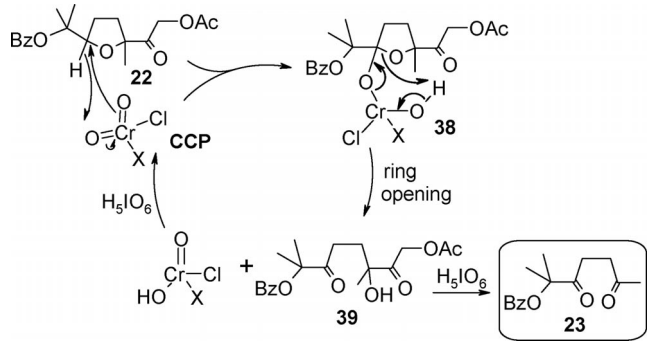
In particular, the presence of the oxidised B ring in **30** strongly suggested that it is formed on the pathway leading to acid **4**, as shown in Scheme 10. On this pathway, acid **4** and ketol **30** would be formed by attack of CCP at the angular C7–H bond in the THF ring B of **2** via intermediates **33**, **34** and **35** as seen for the oxidation of **11**. Compound **35** would follow route a to give acid **4** through the oxidative cleavage of the C7–C8 bond. Alternatively, its oxidative opening would give ketol **30** through route b. The isolation of **30** furnishes the first indirect support for the previously hypothesised[16] formation of chromium diester intermediates, such as **35**, during the oxidative cleavage of enol ethers with PCC, and strongly supports the involvement of enol ether **34**.



Scheme 10. Formation of compounds **4** and **30**.



Scheme 11. A mechanistic explanation for the formation of compounds **31** and **32**.



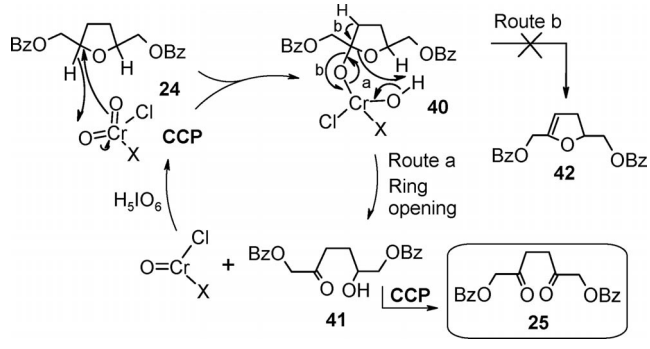
Scheme 12. A catalytic cycle for the formation of diketone **23**.

Acid **3** (see Scheme 3) would in turn originate in a similar way by attack of CCP at the C18–H of the THF ring D in **2** whereas acids **6** and **7** (see Scheme 4) would be formed by attack of the oxidant at the central C ring in the tris-THF **5**.

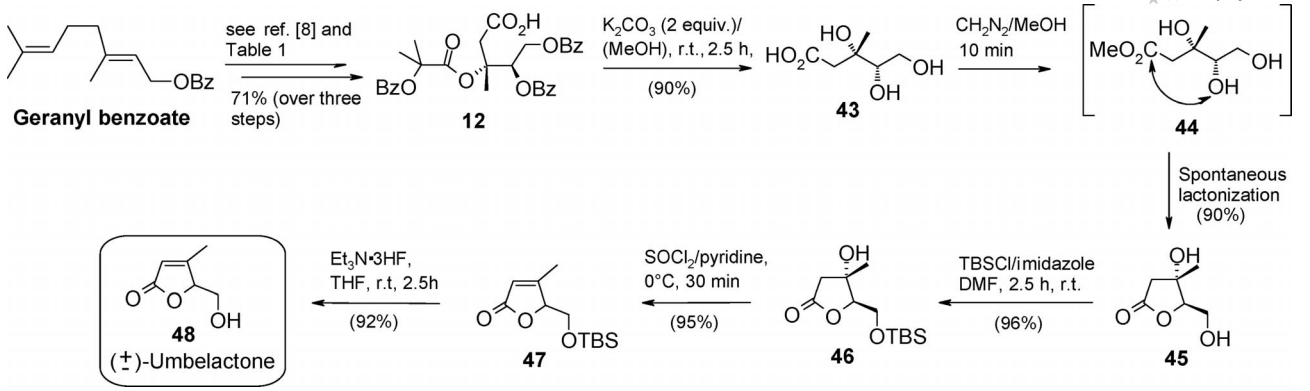
With regard to the minor compounds **31** and **32** (Figure 1), it seems likely that they could originate from **2** in the same route leading to **3** or **4** (Scheme 11). In particular, the oxidative cleavage of the C6–C7 bond in **2** could occur in the chromium ester intermediate **33** through an elimination step now involving both the A and the B rings. This step accounts well for the formation of the C-7 lactone function in **31** with generation once again of an enol ether species, compound **36**, that is then oxidatively cleaved to the dicarbonyl compound **32** via chromium diester **37**, as previously seen. The configuration of **31** has not been determined, so its formation might follow either the depicted route, through attack of the oxidant at the C7-H and oxidation of ring B, or an analogous pathway in which the D ring is oxidised by attack at the C18–H bond (pathway not shown) and cleavage of the C18–C19 bond connecting rings D and E.

By the same line of reasoning, the formation of diketone **23** from **22** (Scheme 12) can be explained by the assumption that the initially formed chromium ester **38** collapses to the dicarbonyl species **39**, the α-ketol portion of which undergoes oxidative cleavage to give **23** through a known process.

The formation of 1,4-diketone **25** from **24** is shown in Scheme 13. In particular, CCP could attack one of the angular C–H bonds in **24** in the usual way to give chromium ester **40**. Opening of this would then follow to give ketol **41** (route a) with simultaneous production of a chromium species, the oxidation of which would regenerate CCP, closing the catalytic cycle. CCP oxidation of the alcohol function in **41**[2a] would eventually give 1,4-diketone **25**. Formation of the related 1,4-diketones **8** (Scheme 4) and **10** (Scheme 6) can be explained in a similar manner. It should be noted that the possible competing path giving rise to an enol ether species (compound **42**, Scheme 13, route b) from **40** is completely suppressed in this case. It is worth noting that the chemical behaviour of PCC in this



Scheme 13. A catalytic cycle for the formation of 1,4-diketone **25**.



Scheme 14. Synthesis of umbelactone.

transformation parallels that displayed by RuO_4. In fact, in a similar transformation, 2,5-dimethyl-tetrahydrofuran is reported to undergo oxidative opening by the RuO_2(cat.)/$NaIO_4$ system to afford hexane-2,5-dione.[17]

Synthesis of Umbelactone

As an application of the developed oxidative procedure, a short synthesis of racemic umbelactone was carried out. Umbelactone is a γ-butenolide natural product, isolated from ethanolic extracts of *Memecylon umbellatum* Brum,[18] that exhibited antiviral activity against the Ranikhet disease virus as well as spasmolytic and antiamphetamine activity. This substance has been the subject of various syntheses both in racemic and in enantiopure form.[19]

Our oxidation of trisubstituted THFs such as **11** described above allows access to elaborated 3,4,5-trioxygenated acids. In particular, compound **12** derived from **11** was seen as a good starting product for the synthesis of umbelactone (Scheme 14). Tribenzoate **12** was converted into trihydroxyacid **43** in high yield by treatment with K_2CO_3 in MeOH. Successive treatment of crude **43** with CH_2N_2 gave transient methyl ester **44**, which spontaneously cyclised to the γ-lactone **45** in 90% yield (81% from **12**). The primary hydroxy group in **45** was then protected as the TBS ether (compound **46**) by treatment with TBSCl/imidazole in DMF (96% yield).[20] Dehydration of **46** was accomplished with $SOCl_2$/pyridine to give silylated umbelactone **47** in 95% yield. Lastly, desilylation of **47** with $Et_3N{\cdot}3HF$ in THF cleanly gave umbelactone **48** (92% yield).

Our synthetic route to umbelactone is short and highly efficient and does not require carbon-carbon bond-forming steps. In addition, it can be made enantioselective to give both the umbelactone enantiomers because mono-THF tribenzoate **11** (Table 1), the immediate precursor of **12**, can be obtained in both enantiomeric forms from commercially available geraniol in high yields and enantiomeric purity.[21] Studies directed towards this goal, as well as exploitation of the above chemistry for the preparation of further functionalised butenolides, are ongoing.

Conclusions

In summary, we have examined the oxidative behaviour of some mono- and poly-THF compounds with the catalytic system PCC (cat.)/H_5IO_6. Novel oxidative pathways leading to the modification/degradation of the THF ring, as well as of the poly-THF backbone, have been disclosed. Plausible hypotheses, consistent with the known reactivity of PCC, have been put forward to explain the new oxidative routes. In particular, attack of the oxidant at the angular C–H bond of the target THF ring with formation of a mixed chromium ester is thought to be the first event. Two main routes then follow. Oxidative carbon-carbon bond cleavage, to give dicarbonyl products, occurs when 2,2,5-trisubstituted THFs are oxidised. The isolation of some minor side products of the process strongly supports the formation of cyclic enol ether intermediates in this transformation. With 2,5-disubstituted mono-THFs, THF ring opening, with no C–C bond cleavage, is observed. 1,4-Diketones, useful building blocks in organic synthesis,[22] are obtained in this case. The latter transformation proceeds with a remarkable, nearly quantitative yield. A third route, leading to the oxidative cleavage of a C-2 side-chain, operates when the THF ring is flanked by a ketone function. Finally, the above results provide further support for the previously observed similarity of the chemical oxidative behaviour of PCC and of RuO_4 toward THF-containing substances.[5a] Further development of the chemistry presented here is currently ongoing.

Experimental Section

General: All reagents were purchased in the highest commercial quality and used without further purification. Petroleum ether had a boiling range of 40–70 °C. Reactions were monitored by thin-layer chromatography carried out on precoated silica gel plates (Merck 60, F_{254}, 0.25 mm thick). Merck silica gel (Kieselgel 40, particle size 0.063–0.200 mm) was used for column chromatography. Na_2SO_4 was used as a drying agent for aqueous workup. HPLC separations were carried out with a Varian 2510 apparatus fitted with a Waters R403 dual cell differential refractometer with use of Phenomenex 250 × 10 mm and 250 × 4.6 mm (both 5 μ) and

LiChrosorb RP-18 250 × 4.0 mm columns. NMR experiments were performed with Varian Unity Inova 700, Varian Unity Inova 500, Varian Mercury Plus 400, and Gemini 200 spectrometers in $CDCl_3$. Proton chemical shifts were referenced to the residual $CHCl_3$ signal (δ =7.26 ppm). ^{13}C NMR chemical shifts were referenced to the solvent (δ =77.0 ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, br, broad. IR spectra were recorded with a Jasco FT-IR 430 spectrophotometer. High-resolution MS was recorded with a Bruker APEX II FT-ICR mass spectrometer with use of ESI. For compounds **2**–**4**, **30** and **31** the numbering previously given[5f] for penta-THF **1** is used.

Syntheses of Poly-THFs 2, 5 and 9: Penta-THF **1**, the tetrol precursor of **5** and dilactone **9** were synthesized as described previously.[5f] Compound **1** was benzoylated as follows. Benzoyl chloride (15 equiv., 6.75 mmol, 785 μL) and DMAP (30 equiv., 3.5 mmol, 11.6 g) were added to **1** (236 mg, 0.45 mmol) dissolved in CH_2Cl_2 (10 mL) and the mixture was stirred at room temp. for 30 h. Water (2 mL) was added and the mixture was stirred for 15 min in a water bath and then taken to dryness. The residue was taken up in CH_2Cl_2 and washed with a sat. $NaHCO_3$ solution and water. The organic phase was dried, filtered and concentrated in vacuo to give an oily product that was chromatographed on silica gel with elution with petroleum ether/Et_2O (8:2) to give dibenzoyl penta-THF **2** (264 mg, 80%). Further purification of **2** was carried out by HPLC (250 × 10 mm column; flow: 2.5 mL min^{-1}, hexane/EtOAc 75:25).

Penta-THF Dibenzoate 2: Oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.05–7.92 (m, 4 H), 7.58–7.35 (m, 6 H), 4.25–4.15 (m, 2 H), 4.02–3.75 (4 H, overlapped multiplets), 2.33–1.49 (20 H, partly overlapped to some methyl protons), 1.64 (s, 3 H), 1.60 (s, 6 H), 1.58, 1.23, 1.16, 1.15, 1.11 (3 H each, singlets, 5× Me) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.54, 165.45, 132.3, 132.2, 131.9, 131.7, 129.2, 128.0, 86.1, 85.7, 85.1, 84.9, 84.4, 84.3, 83.83, 83.78, 83.5, 83.3, 82.5, 34.4, 34.3, 34.1, 32.5, 27.6, 26.9, 26.8, 26.7, 26.5, 24.7, 24.0, 23.4, 23.2, 23.0, 22.6, 21.3, 21.1 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1712 (C=O benzoates), 1285, 710 cm^{-1}. HRMS (ESI): calcd. for $C_{44}H_{60}NaO_9$ $[M + Na]^+$ 755.4135; found 755.4144.

The tris-THF tetrol corresponding to **5** was benzoylated as described for **1**. Benzoyl chloride (15 equiv., 2.6 mmol, 305 μL) and DMAP (60 equiv., 10.4 mmol, 1.3 g) were added to the tetrol (77.0 mg, 0.173 mmol) dissolved in CH_2Cl_2 (2.0 mL) and the mixture was heated at reflux for 10 h. The mixture was worked up as for **1** to give an oily product. Column chromatography on silica gel with elution with petroleum ether/Et_2O (8:2) gave tetrabenzoyl tris-THF **5** (108 mg, 73%).

Tris-THF Tetrabenzoate 5: Oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.16–7.95 (m, 8 H), 7.64–7.45 (m, 4 H), 7.45–7.32 (m, 8 H), 4.54 (dd, J = 6.6, 6.6 Hz, 1 H), 4.32 (m, 5 H), 3.89–3.74 (m, 2 H), 2.33–2.07 (7 H, overlapped multiplets), 2.01–1.73 (13 H, overlapped multiplets) 1.63, 1.57, 1.12, 1.08 (3 H each, singlets, 4× Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.50, 166.46, 165.6, 132.80, 132.78, 132.50, 132.46, 131.7, 131.6, 130.26, 130.24, 129.5, 129.4, 128.26, 128.24, 128.16, 128.15, 85.9, 85.3, 85.2, 84.7, 84.4, 83.9, 83.7, 81.4, 65.2, 65.1, 34.6, 34.4, 31.9, 31.5, 27.5, 27.2, 26.92, 26.86, 24.3, 23.7, 23.5, 23.1, 20.4, 20.0 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1714 (C=O benzoates), 1275, 710 cm^{-1}. HRMS (ESI): calcd. for $C_{52}H_{60}NaO_{11}$ $[M + Na]^+$ 883.4033; found 883.4028.

Oxidation of 2 with PCC/AcOH: PCC (5 equiv., 2.5 mmol, 537 mg) and AcOH (70 equiv., 35 mmol, 2 mL) were added to a solution of **2** (365 mg, 0.50 mmol) in CH_2Cl_2 (16 mL) and the resulting mixture was heated at reflux for 16 h. A saturated aqueous $NaHCO_3$ solution was added and the organic phase was washed with water, dried and concentrated in vacuo to give a yellow oil. Filtration on a silica gel pad (eluent $CHCl_3$/MeOH 9:1) afforded an oily product (350 mg). Further elution with $CHCl_3$/MeOH (8:2) gave a complex mixture of polar products (57 mg) that was not studied further. The first eluted fraction was separated by HPLC (250 × 10 mm column; flow: 2.5 mL min^{-1}; eluent: hexane/EtOAc 75:25) to give unreacted **2** (128 mg) and slightly impure compounds **3** and **4**. Analytical HPLC (250 × 4.6 mm column; flow: 1.0 mL min^{-1}; 3 mg/injection, hexane/EtOAc 75:25) afforded major acid **3** (58.4 mg, 25%, t_R = 11.5 min) and minor acid **4** (16.3 mg, 7%, t_R = 10.0 min).

Acid 3 (Major Isomer): Oil. ^1H NMR (700 MHz, $CDCl_3$): δ = 7.95 (br. d, J = 7.6 Hz, 4 H), 7.52 (br. t, J = 7.4 Hz, 2 H), 7.41 (br. t, J = 7.7 Hz, 4 H), 4.38 (dd, J = 7.3, 7.3 Hz, 1 H), 4.25 (dd, J = 7.4, 7.4 Hz, 1 H), 4.13 (br. dd, J = 7.4, 7.4 Hz, 1 H), 4.01 (dd, J = 10.0, 5.3 Hz, 1 H), 3.94 (dd, J = 9.0, 6.3 Hz, 1 H), 3.25 (d, J = 14.9 Hz, 1 H), 2.97 (d, J = 14.9 Hz, 1 H), 2.36 (ddd, J = 13.0, 8.4, 5.5 Hz, 1 H), 2.07–1.81 (14 H, overlapped multiplets), 1.69 (m, 1 H), 1.62, 1.61, 1.59, 1.56, 1.54, 1.50, 1.20, 1.13 (3 H each, singlets, 8× Me) ppm. ^{13}C NMR (175 MHz, $CDCl_3$): δ = 174.4, 171.9, 165.7, 165.6, 132.6, 132.5, 131.85, 131. 78, 129.42, 129.37, 128.25, 128.20, 86.4, 85.5, 85.3, 84.6, 84.5, 83.9, 83.6, 83.2, 82.8, 81.9, 42.2, 36.5, 34.5, 32.9, 27.9, 27.2, 26.7, 26.6, 26.0, 24.3, 23.14, 23.09, 22.8, 22.3, 21.5, 21.41, 21.38 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3600–2400 (OH), 1714 (C=O of benzoates, ester and acid), 1288, 712 cm^{-1}. HRMS (ESI): calcd. for $C_{44}H_{58}NaO_{12}$ $[M + Na]^+$ 801.3826; found 801.3819.

Acid 4 (Minor Isomer): Oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.9 (br. d, J = 7.4 Hz, 4 H), 7.51 (br. t, J = 7.3 Hz, 2 H), 7.40 (br. t, J = 7.4 Hz, 4 H), 4.35 (dd, J = 7.2, 7.2 Hz, 1 H), 4.24 (dd, J = 9.3, 5.9 Hz, 1 H), 4.07–3.99 (m, 2 H), 3.55 (dd, J = 7.2, 7.2 Hz, 1 H), 3.31 (d, J = 15.0 Hz, 1 H), 2.98 (d, J = 15.0 Hz, 1 H), 2.61–2.53 (m, 1 H), 2.19–2.10 (m, 1 H), 2.05–1.76 (14 H, overlapped multiplets), 1.64, 1.63, 1.60, 1.59, 1.48, 1.47, 1.15, 1.12 (3 H each, singlets, 8× Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.8, 172.9, 165.8, 165.7, 132.6, 132.4, 132.0, 131.7, 129.5, 129.4, 128.19, 128.16, 86.3, 86.0, 85.8, 85.5, 85.1, 84.3, 83.9, 83.8, 83.7, 83.4, 81.5, 43.0, 36.4, 34.7, 34.4, 26.95, 26.88, 26.82, 25.2, 24.1, 23.0, 22.7, 21.7 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3600–2400 (OH), 1712 (C=O of benzoates, ester and acid), 1287, 712 cm^{-1}. HRMS (ESI): calcd. for $C_{44}H_{58}NaO_{12}$ $[M + Na]^+$ 801.3826; found 801.3835.

Oxidation of 2 with PCC (cat.)/H_5IO_6: PCC (2 mol-%, 700 μL of a 0.01 M stock solution in acetonitrile) was added at 0 °C with vigorous stirring to a suspension of H_5IO_6 (4 equiv., 78.8 mg, 0.35 mmol) in acetonitrile (1.5 mL). After 5 min, compound **2** (61 mg, 0.083 mmol) dissolved in acetonitrile (650 μL) was added. After 3 h, CH_2Cl_2 (1.5 mL) was added followed by ethanol (40 μL) and the mixture was taken to dryness. Filtration through a short pad of sodium thiosulfate adsorbed on silica[3] ($CHCl_3$/MeOH 9:1) gave an oily product (50 mg). Further elution with $CHCl_3$/MeOH (8:2) gave a mixture of polar products (14 mg) that was not studied further. The first eluted fraction was separated as described above for the analogous process with PCC/AcOH to give compounds **3** (20.6 mg, 40%) and **4** (2.2 mg, 4%), along with slightly impure ketol **30** (t_R = 5.0 min), lactone **31** (t_R = 13.5 min) and **32** (t_R = 16.5 min). A further reversed-phase HPLC run (250 × 4.0 mm column; flow: 1.0 mL min^{-1}; 2 mg/injection) was required to obtain pure **30** (MeCN/H_2O 9:1, 4.6 mg, 2%, t_R = 14.0 min), **31** (MeCN/H_2O 85:15, 3.0 mg, 2%, t_R = 5.2 min) and **32** (MeCN/H_2O 8:2, 1.0 mg, 1%, t_R = 2.0 min).

Ketol 30: Oil. ^1H NMR (700 MHz, $CDCl_3$): δ = 7.99 (d, J = 6.9 Hz, 2 H), 7.98 (d, J = 6.5 Hz, 2 H), 7.52 (t, J = 7.3 Hz, 2 H), 7.43 (t, J = 7.7 Hz, 2 H), 7.40 (t, J = 7.6 Hz, 2 H), 4.33 (br. s, 1 H, OH), 4.16 (dd, J = 9.2, 6.0 Hz, 1 H), 4.10 (dd, J = 8.2, 7.0 Hz, 1 H), 3.89

(m, 1 H), 3.72 (m, 2 H), 2.66 (ddd, J = 12.7, 10.5, 5.4 Hz, 1 H), 2.55 (d, J = 16.9 Hz, 1 H), 2.44 (d, J = 16.9 Hz, 1 H), 2.18 (ddd, J = 12.3, 9.3, 8.2 Hz, 1 H), 2.03–1.83 (12 H, overlapped multiplets), 1.71–1.61 (m, 2 H), 1.60 (s, 6 H, 2× Me),1.58, 1.55, 1.36, 1.29, 1.14, 1.07 (3 H each, singlets, 6× Me) ppm. ^{13}C NMR (175 MHz, $CDCl_3$): δ = 212.7, 165.8, 165.7, 132.6, 132.4, 132.0, 131.6, 129.6, 129.4, 128.2, 128.1, 101.7, 86.4, 85.9, 85.70, 85.68, 85.65, 84.3, 83.51, 83.46, 83.2, 82.9, 77.8, 48.4, 35.1, 34.4, 31.8, 27.0, 26.86, 26.83, 26.81, 26.0, 24.6, 24.4, 22.82, 22.79, 22.74, 22.2, 21.6, 20.1 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3301 (broad, OH), 1712 (C=O of benzoates and ketone), 1287, 712 cm^{-1}. HRMS (ESI): calcd. for $C_{44}H_{58}NaO_{11}$ [M + Na]$^+$ 785.3877; found 785.3884.

Lactone 31: Oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96 (br. d, J = 7.0 Hz, 2 H), 7.53 (br. t, J = 7.4 Hz, 1 H), 7.41 (br. t, J = 7.5 Hz, 2 H), 4.25 (dd, J = 7.0, 7.0 Hz, 1 H), 3.94 (dd, J = 9.0, 6.2 Hz, 1 H), 3.88 (dd, J = 7.2, 7.2 Hz, 1 H), 3.78 (dd, J = 9.4, 5.1 Hz, 1 H), 2.80 (ddd, J = 17.4, 10.1, 10.2 Hz, 1 H), 2.47 (ddd, J = 17.4, 10.6, 3.5 Hz, 1 H), 2.39 (ddd, J = 13.9, 10.7, 3.5 Hz, 1 H), 2.09–1.65 (13 H, overlapped multiplets), 1.63, 1.58, 1.31, 1.22, 1.11 (3 H each, singlets, 5× Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.6, 165.7, 132.5, 131.9, 129.4, 128.2, 86.5, 85.7, 85.2, 84.6, 84.0, 83.6, 83.4, 82.7, 35.0, 32.7, 29.8, 27.8, 27.3, 26.8, 26.6, 23.5, 23.3, 23.2, 23.0, 22.9, 21.3 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1773 (C=O lactone), 1711 (C=O benzoate), 1288, 1071, 713 cm^{-1}. HRMS (ESI): calcd. for $C_{29}H_{40}NaO_7$ [M + Na]$^+$ 523.2672; found 523.2668.

Acid 32: Oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (br. d, J = 7.3 Hz, 2 H), 7.55 (br. t, 1 H, J = 7.3 Hz), 7.44 (br. t, 2 H, J = 7.7 Hz), 5.62 (dd, 1 H, J = 9.3, 3.1 Hz), 2.86 (dd, 1 H, J = 16.1, 3.2 Hz), 2.74 (dd, 1 H, J = 16.1, 9.4 Hz), 2.11 (s, 3 H), 1.66, 1.65 (3 H each, singlets, 2× Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2, 170.1, 165.1, 133.0, 131.1, 129.5, 128.4, 82.4, 73.9, 34.9, 22.4, 21.7, 20.9 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3600–2400 (OH), 1744 (C=O acetate), 1715 (C=O benzoate and acid), 1283, 712 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{18}NaO_6$ [M + Na]$^+$ 317.1001; found 317.1009.

Oxidation of 5 with PCC (cat.)/H_5IO_6: PCC (1 mol-%, 38 μL of a 0.01 M stock solution in acetonitrile) was added at 0 °C with vigorous stirring to a suspension of H_5IO_6 (4 equiv., 0.15 mmol, 34.2 mg) in acetonitrile (600 μL). After 5 min, compound **5** (32.3 mg, 0.037 mmol) dissolved in acetonitrile (150 μL) was added. After 2 h, a further 1 mol-% PCC was added and the mixture was kept at 0 °C for an additional 1 h. CH_2Cl_2 (700 μL) was then added followed by ethanol (40 μL) and the mixture was taken to dryness. Filtration through a short pad of sodium thiosulfate adsorbed on silica ($CHCl_3$/MeOH 9:1) gave an oily product (19 mg). Separation by HPLC (250 × 4.6 mm column; flow: 1.0 mL min^{-1}; 1 mg/injection, hexane/EtOAc 75:25) gave compounds **6** (10.0 mg, 30%), **7** (2.0 mg, 6%) and **8** (2.9 mg, 9%).

Acid 6 (Major Isomer): Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, J = 8.2 Hz, 4 H), 7.96 (d, J = 8.0 Hz, 4 H), 7.55–7.45 (m, 4 H), 7.44–7.38 (m, 8 H), 5.40 (dd, J = 9.7, 3.1 Hz, 1 H), 4.49 (dd, J = 8.5, 6.2 Hz, 1 H), 4.44 (dd, J = 7.4, 7.4 Hz, 1 H), 4.40–4.28 (4 H, overlapped multiplets), 2.73 (dd, J = 15.8, 3.0 Hz, 1 H), 2.64 (dd, J = 15.8, 9.8 Hz, 1 H), 2.37 (ddd, J = 12.6, 7.9, 6.0 Hz, 1 H), 2.29–2.19 (m, 2 H), 2.17–2.00 (m, 2 H), 1.98–1.58 (12 H, overlapped multiplets), 1.57, 1.55, 1.45, 1.19 (3 H each, singlets, 4× Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 173.4, 166.8, 166.6, 165.8, 165.6, 132.93, 132. 87, 132.7, 131.5, 131.4, 130.26, 130.21, 129.6, 129.55, 129.50, 128.32, 128.27, 85.2, 85.0, 83.9, 83.5, 83.3, 81.3, 75.0, 65.3, 65.0, 36.1, 35.7, 33.7, 31.6, 31.5, 26.9, 25.9, 24.1, 23.5, 23.2, 22.7, 20.4, 20.2 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3600–2400 (OH), 1717 (C=O benzoates, ester and acid), 1279, 1119, 710 cm^{-1}. HRMS (ESI): calcd. for $C_{52}H_{58}NaO_{14}$ [M + Na]$^+$ 929.3724; found 929.3736.

Acid 7 (Minor Isomer): Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (br. d, J = 7.0 Hz, 2 H), 8.02 (br. d, J = 5.5 Hz, 2 H), 7.98 (br. d, J = 8.0 Hz, 4 H), 7.53 (m, 4 H), 7.41 (m, 8 H), 5.41 (dd, J = 6.1, 6.1 Hz, 1 H), 4.64 (dd, J = 7.4, 7.4 Hz, 1 H), 4.49–4.44 (m, 5 H), 2.63 (dd, J = 15.7, 7.3 Hz, 1 H), 2.56 (dd, J = 15.8, 5.9 Hz, 1 H), 2.44 (br. ddd, J = 12.5, 5.5, 5.5 Hz, 1 H), 2.23–1.70 (16 H, overlapped multiplets), 1.64, 1.53, 1.44, 1.28 (3 H each, singlets, 4× Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 171.3, 167.2, 167.0, 165.8, 165.7, 133.03, 132.98, 132.7, 132.6, 131.6, 131.4, 130.1, 129.64, 129.57, 129.4, 128.34, 128.29, 85.3, 84.6, 84.3, 84.1, 83.9, 83.5, 74.9, 65.5, 65.3, 36.5, 35.0, 33.4, 32.0, 31.1, 26.9, 26.3, 24.8, 24.4, 23.6, 23.2, 20.8, 20.6 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3600–2400 (OH), 1714 (C=O benzoates, ester and acid), 1277, 1113, 711 cm^{-1}. HRMS (ESI): calcd. for $C_{52}H_{58}NaO_{14}$ [M + Na]$^+$ 929.3724; found 929.3742.

Diketone 8: Oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.10–7.91 (m, 8 H), 7.62–7.32 (m, 12 H), 4.54–4.24 (6 H, overlapped multiplets), 3.17–2.94 (m, 1 H), 2.94–1.68 (19 H, overlapped multiplets), 1.63 (s, 6 H), 1.37 (s, 3 H), 1.34 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.0, 212.7, 166.5, 165.7, 132.8, 132.7, 131.6, 131.4, 130.35, 130.31, 129.55, 129.53, 129.48, 129.43, 128.35, 128.31, 88.9, 88.7, 84.93, 84.92, 84.2, 83.4, 65.0, 35.2, 34.8, 32.3, 31.8, 30.8, 29.9, 26.3, 24.2, 23.7, 23.55, 23.51, 20.6, 20.4 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1710 (C=O benzoates and ketones), 1274, 1111, 710 cm^{-1}. HRMS (ESI): calcd. for $C_{52}H_{58}NaO_{12}$ [M + Na]$^+$ 897.3826; found 897.3815.

Oxidation of 9: PCC (2 mol-% , 80 μL of a 0.01 M stock solution in acetonitrile) was added at 0 °C with vigorous stirring to a suspension of H_5IO_6 (4 equiv., 0.15 mmol, 35.4 mg) in acetonitrile (600 μL). After 5 min, compound **9** (10.4 mg, 0.039 mmol) dissolved in acetonitrile (150 μL) was added. After 3.5 h, CH_2Cl_2 (750 μL) was added followed by ethanol (40 μL) and the mixture was taken to dryness. Filtration through a short pad of sodium thiosulfate adsorbed on silica ($CHCl_3$/MeOH 9:1) gave almost pure **10** as an oil. Further purification by HPLC (250 × 4.6 mm column; flow: 1.0 mL min^{-1}; $CHCL_3$/MeOH 98:2, tr = 4.0 min) gave pure **10** (4.3 mg, 45%).

Compound 10: Oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.01–2.92 (m, 2 H), 2.92–2.82 (m, 2 H), 2.65–2.53 (m, 6 H), 2.12–2.04 (m, 2 H), 1.55 (s, 6 H, 2× Me) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.2 (2 C), 175.9 (2 C), 89.2 (2 C), 31.3 (2 C), 31.0 (2 C), 28.2 (2 C), 23.6 (2 C) ppm. IR (neat): $\tilde{\nu}_{max}$ = 1774 (C=O lactones), 1717 (C=O ketones) cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{18}NaO_6$ [M + Na]$^+$ 305.1001; found 305.1008.

Synthesis of Mono-THFs 11, 14, 16, 19, 22 and 24: The title compounds were obtained by benzoylation of the corresponding THF diols (synthesized as described previously[5g,5j,8,10]). Purification of these compounds was achieved by column chromatography with the following eluents: **11** (petroleum ether/diethyl ether 9:1), **14** (petroleum ether/diethyl ether 1:1), **16** (petroleum ether/diethyl ether 6:4), **19** (petroleum ether/diethyl ether 1:1), **22** (40:70 petroleum ether/diethyl ether 8:2), **24** (hexane/EtOAc 8:2).

Compound 11: Oil. ^{1}H NMR: (200 MHz, $CDCl_3$): δ = 8.13–7.88 (m, 6 H), 7.68–7.28 (m, 9 H), 5.65 (dd, J = 8.8, 2.9 Hz, 1 H), 4.80 (dd, J = 12.2, 2.9 Hz, 1 H), 4.59 (dd, J = 12.2, 8.8 Hz, 1 H), 4.33 (dd, J = 6.3 Hz, 1 H), 2.27–1.74 (m, 4 H), 1.67 (s, 3 H), 1.64 (s, 3 H), 1.43 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.4, 166.0, 165.6, 133.0, 132.9, 132.5, 131.6, 129.8, 129.65 (2 C), 129.63, 129.5 (2 C), 129.3 (2 C), 128.4 (2 C), 128.3 (2 C), 128.2 (2 C), 83.5,

83.0, 82.8, 76.2, 63.9, 34.6, 26.9, 23.6, 23.2, 21.3 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1719 (C=O benzoates), 1281, 1111, 709 cm^{-1}. HRMS (ESI): calcd. for $C_{31}H_{32}NaO_7$ $[M + Na]^+$ 539.2046; found 539.2038.

Compound 14: Oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.00 (m, 4 H), 7.66–7.30 (m, 6 H), 5.46 (dd, J = 8.8, 2.6 Hz, 1 H), 4.78–4.20 (5 H, overlapped multiplets), 2.15–1.88 (10 H, including two acetate singlets at 2.02 and 1.96), 1.67 (s, 3 H), 1.36 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.9, 170.5, 166.1, 165.6, 133.1, 132.8, 131.0, 129.7 (2 C), 129.6 (3 C), 128.5 (2 C), 128.3 (2 C), 83.2, 83.0, 80.4, 76.1, 65.2, 63.3, 34.5, 26.8, 23.5, 20.80 (2 C), 18.9 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1740 (C=O acetates), 1721 (C=O benzoates), 1275, 712 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{32}NaO_9$ $[M + Na]^+$ 535.1944; found 535.1963.

Compound 16: Oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.07 (d, J = 8.5 Hz, 2 H), 7.96 (d, J = 7.1 Hz, 2 H), 7.64–7.29 (m, 6 H), 5.20 (s, 1 H), 4.33 (dd, J = 7.7, 6.9 Hz, 1 H), 3.72 (s, 3 H), 2.56–2.38 (m, 1 H), 2.19–1.75 (m, 3 H), 1.61 (s, 3 H), 1.59 (s, 3 H), 1.46 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.6, 166.0, 165.7, 133.3, 132.5, 131.6, 129.8 (3 C), 129.4 (2 C), 128.4 (2 C), 128.2 (2 C), 83.5, 83.3, 82.8, 78.0, 52.2, 34.3, 26.5, 23.4, 23.0, 21.3 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1713 (C=O benzoates and CO_2Me), 1285, 1113, 710 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{28}NaO_7$ $[M + Na]^+$ 463.1733; found 463.1717.

Compound 19: Oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.07 (d, J = 7.7 Hz, 2 H), 7.96 (d, J = 8.2 Hz, 4 H), 7.64–7.30 (m, 9 H), 5.65 (dd, J = 8.6, 2.7 Hz, 1 H), 4.75 (dd, J = 11.9, 2.8 Hz, 1 H), 4.55 (dd, J = 11.9, 8.6 Hz, 1 H), 4.32 (dd, J = 8.1, 6.6 Hz, 1 H), 2.27–1.68 (m, 4 H), 1.60 (s, 6 H), 1.45 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.5, 166.0, 165.7, 133.04, 133.02, 132.4, 131.9, 130.1, 129.72 (2 C), 129.70, 129.6 (2 C), 129.4 (2 C), 128.4 (2 C), 128.3 (2 C), 128.2 (2 C), 85.5, 83.03, 83.01, 76.1, 64.0, 34.8, 26.7, 24.1, 22.6, 21.5 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1712 (C=O benzoates), 1278, 1109, 708 cm^{-1}. HRMS (ESI): calcd. for $C_{31}H_{32}NaO_7$ $[M + Na]^+$ 539.2046; found 539.2055.

Compound 22: Oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.96–7.87 (d, J = 6.9 Hz, 2 H), 7.59–7.35 (m, 3 H), 5.04 (AB system, J = 17.8 Hz, 2 H), 4.20 (dd, J = 7.2 Hz, 1 H), 2.54–2.39 (m, 1 H), 2.13–1.77 (6 H, overlapped multiplets including the acetate singlet at 2.08), 1.71 (s, 3 H), 1.61 (s, 3 H), 1.41 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 206.5, 170.2, 165.7, 132.7, 131.4, 129.3 (2 C), 128.4 (2 C), 88.5, 85.9, 82.7, 65.7, 35.4, 26.0, 23.6, 22.8, 22.6, 20.4 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1735 (C=O acetate), 1716 (C=O benzoate and ketone), 1289, 712 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{24}NaO_6$ $[M + Na]^+$ 371.1471; found 371.1489.

Compound 24: Oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.05 (br. d, J = 8.4 Hz, 4 H), 7.55 (br. t, J = 7.4 Hz, 2 H), 7.42 (br. t, J = 7.8 Hz, 4 H), 4.42 (2 H, overlapped multiplets), 4.39–4.32 (4 H, overlapped multiplets), 2.12 (m, 2 H), 1.89 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.4 (2 C), 132.9 (2 C), 130.0 (2 C), 129.6 (4 C), 128.3 (4 C), 77.5 (2 C), 66.6 (2 C), 27.8 (2 C) ppm. IR (neat): $\tilde{\nu}_{max}$ = 1715 (C=O benzoates), 1268, 709 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{20}NaO_5$ $[M + Na]^+$ 363.1208; found 363.1220.

Synthesis of 20: K_2CO_3 (2 equiv., 0.4 mmol, 55 mg) was added to compound **11** (106 mg, 0.20 mmol) dissolved in MeOH (5 mL) and the mixture was stirred at room temp. for 1.5 h. Water (1 mL) was added followed by acetic acid up to neutrality. The mixture was taken to dryness in vacuo and the solid was partitioned between a sat. $NaHCO_3$ solution and EtOAc. The organic phase was washed with water, dried and concentrated to give an oily product (65.9 mg).

$NaIO_4$ supported on wet silica (2.4 equiv., 0.47 mmol, 746 mg; 0.64 mmol g^{-1}) was added to the crude product obtained above, dissolved in CH_2Cl_2 (5 mL), and the mixture was stirred for 30 min at room temp. The reaction mixture was filtered, the solid was thoroughly washed with CH_2Cl_2, and the filtrate was taken to dryness to give an oily product.

Sodium borohydride (two spatula tips) was added to the above oil (55.1 mg), dissolved in EtOH (4 mL). After 30 min, acetic acid was added dropwise until no gas evolution was observed. The mixture was filtered and the filtrate was taken to dryness to give an oily product.

The above oil (33.0 mg, 0.12 mmol) was dissolved in pyridine (500 μL) and benzoyl chloride (1.1 equiv., 0.13 mmol, 15 μL) was added. After 1 h, water (100 μL) was added and the mixture was taken to dryness. Purification by preparative TLC (hexane/EtOAc 1:1) yielded pure **20** (33.0 mg, 43% over four steps).

Compound 20: Oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.06 (d, J = 7.0 Hz, 2 H), 7.98 (d, J = 6.9 Hz, 2 H), 7.61–7.33 (6 H, overlapped multiplets), 4.38 (d, J = 11.1 Hz, 1 H), 4.31 (m, 1 H), 4.20 (d, J = 11.1 Hz, 1 H), 2.20–1.73 (m, 4 H), 1.64 (s, 3 H), 1.61 (s, 3 H), 1.38 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.4, 165.7, 133.0, 132.5, 131.7, 130.1, 129.5 (2 C), 129.4 (2 C), 128.3 (2 C), 128.2 (2 C), 83.8, 83.4, 81.8, 69.7, 34.5, 26.8, 24.1, 23.0, 21.4 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1712 (C=O benzoates), 1277, 1112, 709 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{26}NaO_5$ $[M + Na]^+$ 405.1678; found 405.1670.

General Reaction Procedure for the Oxidation of Mono-THF Compounds 11, 14, 16, 19, 20, 22 and 24: PCC (5 mol-%, from a 0.01 M stock solution in acetonitrile) was added at room temp. with vigorous stirring to a suspension of H_5IO_6 (4 equiv.) in acetonitrile. After 5 min the mono-THF compound (1 equiv.) dissolved in acetonitrile was added. The overall volume of acetonitrile was such that the final concentration of the solution was 0.05 M. After complete consumption of the starting material (TLC monitoring, usually 45–60 min), ethanol (excess) was added and stirring was continued until the colour of the solution had turned from yellow to green. Silica (excess) was then added and the solvent was evaporated in vacuo to give a fine powder that was loaded on the top of a silica gel column. Elution with $CHCl_3$/MeOH (9:1) allowed recovery of the acid that proved to be pure enough for successive spectral studies and/or synthetic steps.

Compound **11** (112.0 mg, 0.22 mmol) was subjected to the standard oxidative procedure to give the crude acid as a yellow oil. It was purified by column chromatography (CH_2Cl_2/MeOH 95:5) to yield **12** (99 mg, 80%) and lactone **13** (8.0 mg, 10%) as oils.

Compound 12: Oil. ^1H NMR: (200 MHz, $CDCl_3$): δ = 8.00 (d, J = 7.7 Hz, 2 H), 7.87 (m, 4 H), 7.57–7.28 (m, 9 H), 5.89 (dd, J = 7.8, 3.1 Hz, 1 H), 4.74 (dd, J = 12.2, 3.1 Hz, 1 H), 4.45 (dd, J = 12.2, 7.8 Hz, 1 H), 3.24 (AB system, J = 15.6 Hz, 2 H), 1.86 (s, 3 H), 1.71 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.1, 171.1, 166.0, 165.5, 165.2, 133.15, 133.12, 133.0, 129.8, 129.6 (6 C), 129.5, 129.3, 128.35 (4 C), 128.28 (2 C), 82.0, 79.0, 74.6, 62.8, 39.2, 24.55, 24.46, 21.3 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3600–2400 (OH), 1717 (C=O benzoates, ester and acid), 1282, 1107, 709 cm^{-1}. HRMS (ESI): calcd. for $C_{31}H_{30}NaO_{10}$ $[M + Na]^+$ 585.1737; found 585.1723.

Compound 13: Oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.04 (d, J = 7.9 Hz, 2 H), 7.92 (d, J = 8.0 Hz, 2 H), 7.67–7.31 (m, 6 H), 5.66 (dd, J = 8.3, 3.2 Hz, 1 H), 4.85 (dd, J = 12.1, 3.2 Hz, 1 H), 4.52 (dd, J = 12.1, 8.3 Hz, 1 H), 2.61 (t, J = 7.6 Hz, 2 H), 2.37 (ddd, J = 13.1, 7.6, 7.6 Hz, 1 H), 2.08 (ddd, J = 13.1, 9.5, 9.5 Hz, 1 H), 1.66 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 176.2, 166.2, 165.5, 133.7, 133.2, 129.9 (2 C), 129.6 (2 C), 129.4, 128.9, 128.7 (2 C), 128.4 (2 C), 85.2, 75.6, 62.8, 31.5, 28.9, 24.2 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1778 (C=O lactone), 1721 (C=O benzoates), 1259, 709 cm^{-1}.

HRMS (ESI): calcd. for $C_{21}H_{20}NaO_6$ [M + Na]$^+$ 391.1158; found 391.1167.

Compound **14** (13.5 mg, 0.026 mmol) was subjected to the standard oxidative procedure to give the crude acid as an oil. This was purified by column chromatography (CH_2Cl_2/MeOH 95:5) to yield **15** (9.4 mg, 65%) as an oil.

Compound 15: Oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.0 (m, 4 H), 7.65–7.29 (m, 6 H), 5.75 (dd, J = 7.8, 2.9 Hz, 1 H), 4.67–4.49 (m, 3 H), 4.21 (dd, J = 12.1, 7.8 Hz, 1 H), 3.20 (AB system, J = 15.7 Hz, 2 H), 2.09 (s, 3 H, acetate), 1.94 (s, 3 H, acetate), 1.85 (s, 3 H), 1.73 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.4, 172.3, 170.5, 170.3, 165.24, 165.17, 133.4, 133.3, 130.1, 129.8 (2 C), 129.7 (2 C), 129.6, 128.5 (4 C), 82.8, 79.4, 74.3, 66.0, 62.2, 38.9, 21.1, 20.71, 20.68, 19.7 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3600–2400 (OH), 1740 (shoulder, C=O acetates) 1721 (C=O benzoates, ester and acid), 1273, 1226, 711 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{30}NaO_{12}$ [M + Na]$^+$ 581.1635; found 581.1651.

Compound **16** (23.8 mg, 0.050 mmol) was subjected to the standard oxidative procedure to give an oil, which was separated by column chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 95:5) to yield acid **17** (7.3 mg, 30%) and lactone **18** (6.4 mg, 45%) as oils.

Compound 17: Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02–7.89 (m, 4 H), 7.61–7.44 (m, 2 H), 7.44–7.29 (m, 4 H), 5.69 (s, 1 H), 3.64 (s, 3 H), 3.42 (d, J = 16.2 Hz, 1 H), 3.27 (d, J = 16.2 Hz, 1 H), 1.91 (s, 3 H), 1.65 (s, 3 H), 1.63 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 171.0, 167.4, 165.4, 165.2, 133.4, 133.1, 130.2, 129.85, 129.84 (2 C), 129.6 (2 C), 128.4 (2 C)128.2 (2 C), 81.1, 78.8, 75.8, 52.4, 39.0, 24.6, 24.1, 20.7 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3600–2400 (OH), 1719 (C=O benzoates, esters and acid), 1287, 1110, 712 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{26}NaO_{10}$ [M + Na]$^+$ 509.1424; found 509.1418.

Compound 18: Oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.06, (d, J = 7.0 Hz, 2 H), 7.63 (t, J = 6.5 Hz, 1 H), 7.48 (t, J = 7.7 Hz, 2 H), 5.26 (s, 1 H), 3.80 (s, 3 H), 2.76–2.52 (m, 3 H), 2.20–2.01 (m, 1 H), 1.65 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.6, 167.3, 165.5, 133.8, 129.9 c, 128.6 (3 C), 84.3, 77.2, 52.9, 30.9, 28.7, 23.8 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1781 (C=O lactone), 1726 (C=O benzoate and CO_2Me), 1271, 1112, 714 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{16}NaO_6$ [M + Na]$^+$ 315.0845; found 315.0853.

Compound **19** (9.7 mg, 0.019 mmol) was subjected to the standard oxidative procedure to give the crude acid as an oil. This was purified by column chromatography (CH_2Cl_2/MeOH 95:5) to yield **12** (7.3 mg, 70%).

Compound **20** (31.0 mg, 0.081 mmol) was subjected to the standard oxidative procedure to give the crude acid as an oil. This was purified by column chromatography (CH_2Cl_2/MeOH 95:5) to yield **21** (21.5 mg, 65%) as an oil.

Compound 21: Oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.94 (m, 4 H), 7.60–7.44 (m, 2 H), 7.42–7.28 (m, 4 H), 4.60 (AB system, J = 11.7 Hz, 2 H), 3.12 (br. s, 2 H), 1.71 (s, 3 H), 1.64 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.9, 171.3, 165.8, 165.4, 133.05, 133.02, 129.8, 129.65, 129.6 (2 C), 129.5 (2 C), 128.35 (2 C), 128.30 (2 C), 80.4, 78.9, 67.5, 39.9, 24.5 (2 C), 21.0 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3600–2400 (OH), 1716 (C=O benzoates, ester and acid), 1284, 1109, 710 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{24}NaO_8$ [M + Na]$^+$ 451.1369; found 451.1360.

Compound **22** (10.1 mg, 0.029 mmol) was subjected to the standard oxidative procedure to give an oil, which was purified by HPLC (hexane/EtOAc 7:3) to yield 1,4-diketone **23** (5.3 mg, 70%), as an oil.

Compound 23: Oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.04 (d, J = 8.3 Hz, 2 H), 7.59 (t, J = 7.2 Hz, 1 H), 7.45 (t, J = 7.7 Hz, 2 H), 2.78 (m, 4 H), 2.19 (s, 3 H), 1.65 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 207.8, 207.3, 165.9, 133.4, 129.8 (2 C), 129.4, 128.4 (2 C), 84.2, 37.0, 30.1, 30.0, 23.8 (2 C) ppm. IR (neat): $\tilde{\nu}_{max}$ = 1715 (C=O benzoate and ketones), 1287, 714 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{18}NaO_4$ [M + Na]$^+$ 285.1103; found 285.1109.

Compound **24** (107.0 mg, 0.31 mmol) was subjected to the standard oxidative procedure with PCC (2 mol-%) to give 1,4-diketone **25** (109 mg, 98%).

Compound 25: Amorphous solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.09 (d, J = 7.2 Hz, 4 H), 7.58 (t, J = 7.5 Hz, 2 H), 7.45 (t, J = 7.7 Hz, 4 H), 4.95 (s, 4 H), 2.87 (s, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 202.7 (2 C), 165.8 (2 C), 133.5 (2 C), 129.9 (4 C), 129.0 (2 C), 128.4 (4 C), 68.3 (2 C), 32.0 (2 C) ppm. IR (neat): $\tilde{\nu}_{max}$ = 1713 (C=O benzoates and ketones), 1275, 715 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{18}NaO_6$ [M + Na]$^+$ 377.1001; found 377.1015.

Synthesis of Umbelactone

Trihydroxy Acid 43: K_2CO_3 (2.0 equiv. 58 mg, 0.42 mmol) was added to acid **12** (118.1 mg, 0.21 mmol), dissolved in MeOH (5 mL), and the mixture was stirred at room temp. for 2.5 h. Water (1 mL) was added followed by acetic acid up to neutrality. The mixture was taken to dryness in vacuo and the solid was partitioned between a sat. $NaHCO_3$ solution and EtOAc. The organic phase was washed with water, dried and concentrated to give **43** (31.2 mg, 90%), which was used in the next step without further purification.

Compound 43: ^{1}H NMR (500 MHz, CD_3OD): δ = 3.78 (dd, J = 10.9, 2.5 Hz, 1 H), 3.58 (dd, J = 10.9, 7.9 Hz, 1 H), 3.53 (dd, J = 7.9, 2.5 Hz, 1 H), 2.49 (d, J = 14.9 Hz, 1 H), 2.35 (d, J = 14.9 Hz, 1 H), 1.36 (s, 3 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 180.6, 79.0, 73.5, 63.9, 45.6, 24.7 ppm. HRMS (ESI): calcd. for $C_6H_{12}NaO_5$ [M + Na]$^+$ 187.0582; found 187.0590.

Dihydroxylactone 45: Excess CH_2N_2 in Et_2O was added to trihydroxy acid **43** (30.0 mg, 0.18 mmol), dissolved in MeOH (4 mL), until a yellow colour persisted. The mixture was stirred for a further 10 min and the excess of CH_2N_2 was then destroyed by dropwise addition of acetic acid until the solution became colourless. The mixture was taken to dryness to give an oil, which was purified by column chromatography (CH_2Cl_2/MeOH 9:1) to yield lactone **45** (23.5 mg, 90%) as a clear oil.

Compound 45: Oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.30 (dd, J = 6.0, 4.4 Hz, 1 H), 3.86 (m, 2 H), 2.77 (d, J = 17.2 Hz, 1 H), 2.50 (d, J = 17.2 Hz, 1 H), 1.44 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 177.9, 90.1, 75.7, 61.0, 45.6, 24.5 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3408 (broad, OHs), 1771 (C=O lactone) cm^{-1}. HRMS (ESI): calcd. for $C_6H_{10}NaO_4$ [M + Na]$^+$ 169.0477; found 169.0472.

Silylated Lactone 46: Imidazole (3.0 equiv., 28.6 mg, 0.42 mmol) and *tert*-butyldimethylsilyl chloride (1.5 equiv., 31.5 mg, 0.21 mmol) were added to lactone **45** (21.3 mg, 0.14 mmol), dissolved in DMF (300 µL), and the mixture was stirred for 2.5 h at room temp. MeOH (500 µL) was then added and stirring was continued for 30 min. The reaction mixture was concentrated on silica and purified by column chromatography (hexane/EtOAc 1:1) to yield compound **46** (34.9 mg, 96%) as a clear oil.

Compound 46: Oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.19 (dd, J = 3.8, 2.8 Hz, 1 H), 4.12 (dd, J = 11.8, 2.8 Hz, 1 H), 4.02 (dd, J = 11.8, 3.8 Hz, 1 H), 3.66 (br. s, 1 H), 2.73 (d, J = 17.6 Hz, 1 H), 2.57 (d, J = 17.6 Hz, 1 H), 1.49 (s, 3 H), 0.90 (s, 9 H), 0.12 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.7, 85.5, 75.4, 61.8,

44.9, 26.7, 25.7 (3 C), 18.1, –5.6, –5.7 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3447 (broad, OH), 1782 (C=O lactone) cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{24}NaO_4Si$ $[M + Na]^+$ 283.1342; found 283.1339.

Unsaturated Lactone 47: Thionyl chloride (5 equiv., 0.55 mmol, 40 μL) was added to lactone **46** (30.0 mg, 0.11 mmol), dissolved in pyridine (500 μL), and the mixture was stirred at 0 °C for 30 min. Water (500 μL) was added and the reaction mixture was evaporated in vacuo to give an oily product. Column chromatography (hexane/EtOAc 8:2) yielded compound **47** (25.3 mg, 95%) as a clear oil.

Compound 47: Oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.83 (br. s, 1 H), 4.82 (br. s, 1 H), 3.94 (dd, J = 11.3, 3.7 Hz, 1 H), 3.90 (dd, J = 11.3, 3.5 Hz, 1 H), 2.10 (s, 3 H), 0.85 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.2, 166.7, 118.1, 84.7, 61.7, 25.7 (3 C), 18.1, 14.1, –5.5, –5.6 ppm. IR (neat): $\tilde{\nu}_{max}$ = 1759 (C=O α,β-unsaturated lactone), 1132, 837, 778 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{22}NaO_3Si$ $[M + Na]^+$ 265.1236; found 265.1244.

Umbelactone (48): $Et_3N{\cdot}3\,HF$ (20 equiv., 270 μL) was added to lactone **47** (20.2 mg, 0.083 mmol), dissolved in dry THF (1 mL), and the mixture was stirred for 2.5 h at room temp. Et_3N (500 μL) was then added and the mixture was taken to dryness. The residue was co-evaporated with Et_3N (2 × 500 μL) and MeOH (3 × 500 μL) and concentrated to give an oil, which was purified by column chromatography (EtOAc) to yield umbelactone **48** (9.8 mg, 92%) as a clear oil.

Compound 48: Oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.89 (br. s, 1 H), 4.91 (br. s, 1 H), 4.07 (dd, J = 12.7, 2.9 Hz, 1 H), 3.77 (dd, J = 12.7, 3.9 Hz, 1 H), 2.11 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.8, 165.8, 118.3, 85.0, 61.5, 14.0 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3404 (broad OH), 2921, 2851, 1731 (broad, C=O α,β-unsaturated lactone), 1647, 1050 cm^{-1}. HRMS (ESI): calcd. for $C_6H_8NaO_3$ $[M + Na]^+$ 151.0371; found 151.0375.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra.

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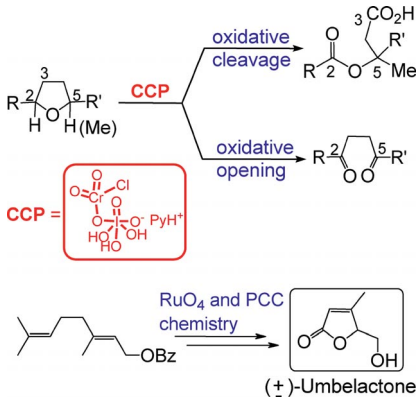
Catalytic Oxidation

The catalytic oxidation of mono- and polytetrahydrofuran compounds has been carried out with chlorochromatoperiodate (CCP), generated by the combination of PCC and H_5IO_6. New synthetically useful oxidative transformations are disclosed. Umbelactone, an antiviral natural butenolide metabolite, has been synthesized by use of the developed chemistry.



Keywords: Oxidation / Oxygen heterocycles / Reaction mechanisms

