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Pyridinium chlorochromate chemistry. New insight into oxidation of tetrahydrofurans

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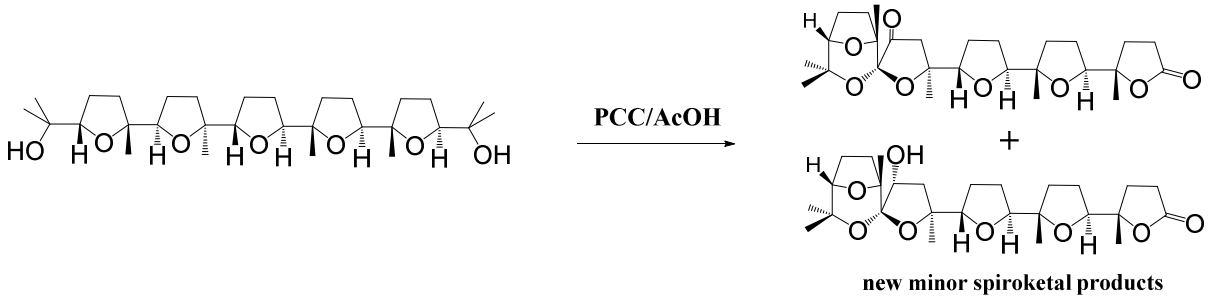
Abstract

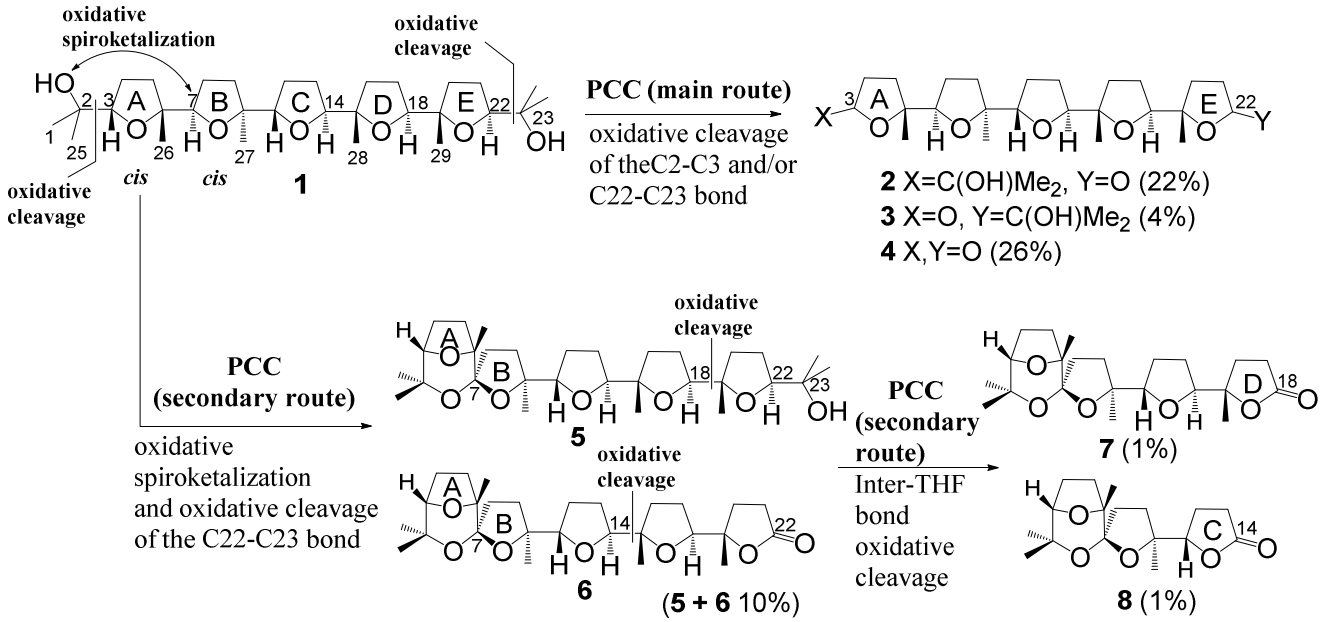
A thorough investigation of the minor oxidation products of two penta-tetrahydrofuran compounds with pyridinium chlorochromate has been carried out. Isolation of ring-B oxygenated spiroketal and degradation products, including polycyclic mono- and bis-lactone compounds, supports the previously postulated involvement of cyclic enolether intermediates in the oxidation of THF and poly-THF substances with PCC. Based on the collected evidence, a new mechanistic route for the PCC-mediated oxidative cleavage of α-hydroxy-THF compounds to γ-lactones has been postulated. The proposed mechanism well agrees with the one reported for the oxidative cleavage of 8-hydroxy-neoisocedranol oxide by RuO_4, a fact that further supports our previous observation on the similar oxidizing behaviour shown by PPC and RuO_4 towards THF-containing compounds.



Keywords: Pyridinium chlorochromate, oxidation, spiroketals, mechanistic insight

Introduction

Pyridinium chlorochromate (PCC) is a well known oxidizing reagent employed in a number of processes.[1,2] Though the most popular process mediated by PCC is the oxidation of primary and secondary alcohols to aldehyde and ketones, respectively, many other functional groups undergo PCC oxidation. As a continuation of our interest in oxidative processes mediated by transition metal oxo-species[3-11] as well as in the synthesis and derivatization of new THF-containing compounds,[12-21] we recently focused on oxidation processes mediated by PCC. These studies led to the discovery of new interesting transformations including oxidative spiroketalization,[22] oxidative cleavage of trisubstituted mono-THF compounds[23] and synthesis of bis-α-acyloxy-1,4- and 1,5-diketones from THF and THP-diols, respectively.[24] During these studies evidence on some similarities about the oxidative behaviour of PCC and RuO_4 were also recorded. In particular, we have previously reported[22] that penta-THF **1**[17,20] (Scheme 1), when treated with PCC furnishes the new compounds **2-8** four of which (**5**-**8**) representative of a novel class of poly-THF spiroketals displaying antitumor activity on breast and ovarian cancer cell lines.[22]



Scheme 1. A new type of spiroketal compounds obtained by PCC-mediated oxidation of penta-THF compound **1**.

Inspection of the structure of these substances reveals that compound **1** undergoes three types of oxidative processes all involving the interaction of the oxidant with different THF ether methine groups:

a) The oxidative cleavage of the C2-C3 and/or C22-C23 bonds in **1** give rise to lactones **2** and **4**, the main oxidation products;

b) The oxidative spiroketalization, formally involving the C(2)OH group and the C-7 carbon at the *cis*-*cis* bis-THF terminus of the poly-THF chain, gives rise to the spiroketal-containing compound **5**, possessing the intact carbon skeleton of **1**. The terminal lactone in the related spiro-compound **6**, in turn, arises from the further oxidative cleavage of the C22-C23 bond in **5**, according to the route highlighted in point a;

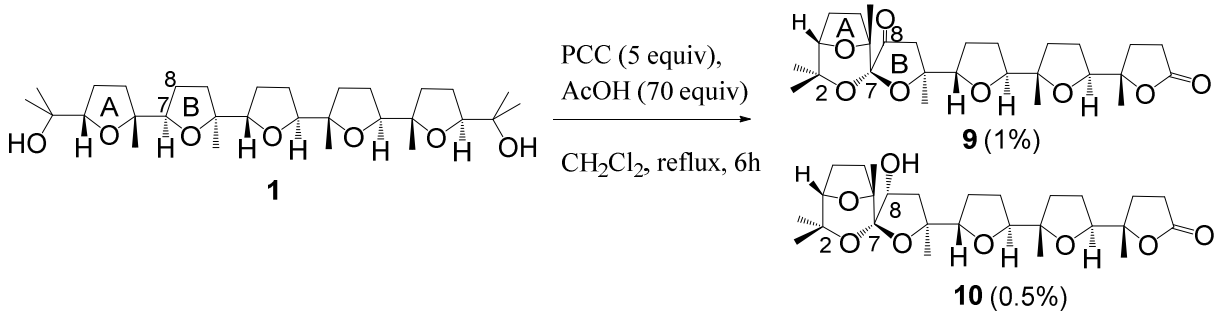
c) The inter-THF C-C oxidative bond cleavage in **5** and/or **6** is responsible of the formation of the degraded, minor, spiro-compounds **7** and **8**.

The transformations highlighted in points a and b point out the similarity of the oxidizing behaviour of PCC with the one displayed by RuO_4 which catalyzes similar processes by reaction with **1**.[13]

The PCC-mediated conversion of β-hydroxy mono- and poly-THF compounds to γ-lactones (see for example conversion of **1** to **2**-**4** or **5** to **6** in Scheme 1) is a well-documented process[14,17,25-31] although no definitive proof on the cleavage mechanism has been provided. On the other hand, spirocyclization leading to compounds **5**-**8** is a novel transformation which is attractive both from a mechanistic and applicative point of view. Therefore, we were interested to collect further evidence on these processes and, more in general, on the other oxidative routes depicted in Scheme 1. To this end, a careful analysis of the minor side-products formed during the oxidation of **1**, and the corresponding dibenzoate, with PCC was undertaken. This survey allowed the identification of novel pathways working in the oxidation of differently substituted tetrahydrofurans with PCC, or allowed to confirm previously formulated mechanistic hypotheses on some PCC-mediated processes.[22,23] In addition, based on the acquired evidence, we could formulate a new plausible mechanistic route on the PCC-mediated oxidative cleavage of THF rings bearing a α tertiary alcohol function,[14,17,25-33] such as **1** and **2**, to the corresponding γ-lactones, that well agrees with the mechanism proposed for the analogous process mediated by RuO_4.

Results and Discussion

C-8 oxygenated spiroketals. Penta-THF **1** was synthesized from squalene according to a previously described procedure[17] and its purity checked by direct and reversed-phase HPLC and high-field NMR analysis to exclude the presence of minor impurities. The oxidation of **1** in the presence of PCC was carried out in CH_2Cl_2 at reflux as previously described.[22] The crude reaction mixture was subjected to a careful preparative and, when required, to analytical HPLC to give the new C-8 oxygenated spiroketals **9** and **10** (Scheme 2) as well as some poly-THF dilactone compounds (**12**-**14**, see later Scheme 4) derived from the oxidative degradation of the carbon skeleton of **1**, besides previously isolated compounds **2**-**8** (Scheme 1).



Scheme 2. Minor C-8 oxygenated spiroketal compounds obtained by PCC-mediated oxidation of **1**.

Determination of the stereostructure of the 8-oxo-compound **9** was accomplished by registration of a full set of high-field 2D-NMR spectra while the structure of the corresponding C-8 alcohol **10** was inferred by chemical correlation with **9** and NMR evidence. In particular, the configuration of the C-7 spiro-centre belonging to the tricyclic spiroketal subunit in **9** was established to be the same found in related spiro-compounds **5**-**8** (Scheme 1) through unambiguous ROESY evidence (Figure 1).

The structural relationship between **9** and the corresponding alcohol **10** was proven by sodium borohydride reduction of **9** that gave alcohol **10** (10%, Scheme 3), through attack of the reducing agent to the carbonyl plane from its upper face, along with the corresponding triol **11** (75%), derived from the further reduction of the γ-lactone function in **9**. Configuration at C-8 in **10** was established based on 2D-NMR studies carried out on the corresponding triol **11**, available in higher amounts, having ascertained the sterostructural relationship between the two compounds by borohydride reduction of the former to the latter (Scheme 3). In particular, a significant ROESY correlation peak between Me-26 and H-8 (Figure 1) established the α-orientation of the OH group in this compound and thus its cis stereostructural relationship with the oxygen bridging C-2 and C-7 in the F ring, a fact having important mechanistic implications, as discussed later.

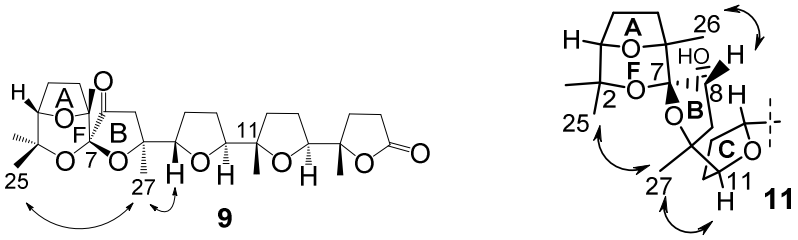
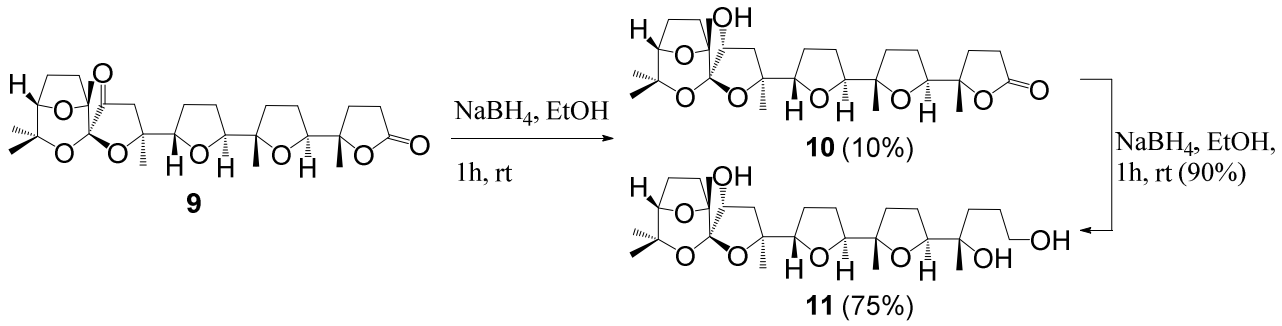
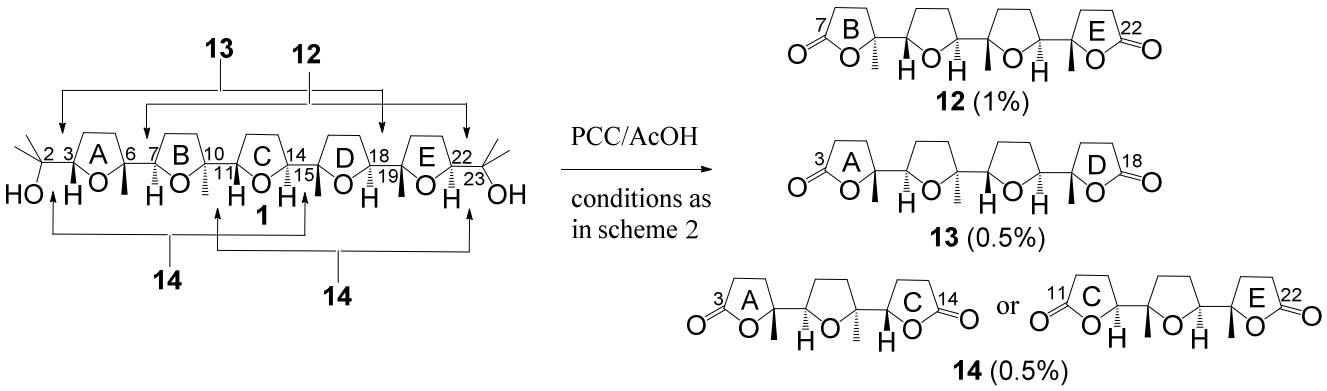


Figure 1. Some ROESY correlations of **9** (left) and a stereo-view of the spiroketal-containing portion of **10** showing significant ROESY correlations (right).



Scheme 3. Borohydride reduction of the 8-oxo-spirocompound **9**.

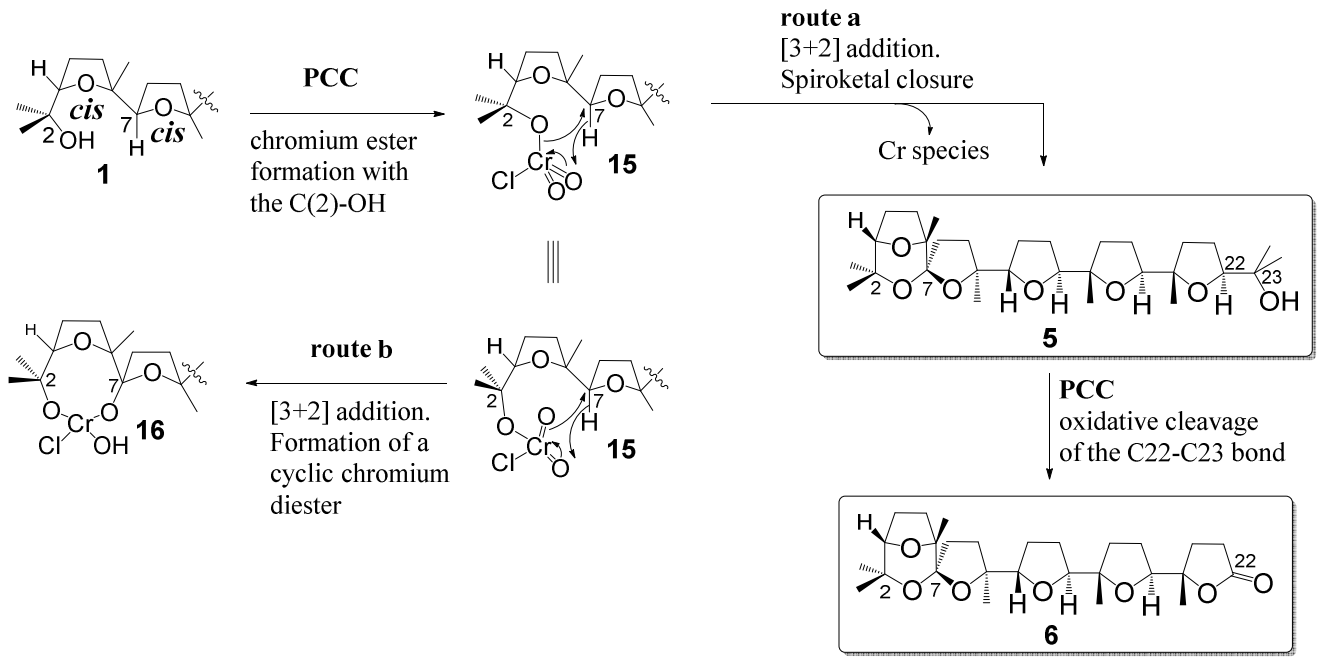
Dilactones. Dilactones **12**-**14** (Scheme 4), derived from the cleavage of the poly-THF skeleton of **1** at different hydrogen-carrying ether positions, were also isolated as minor products (overall 2% yield) from the oxidation of **1** with PCC. Their stereostructures were determined by 2D-NMR studies, including ROESY experiments. The *trans* configuration of both the THF rings in the most abundant compound **12** (1%), indicated it to originate from the oxidative cleavage of **1** at the C6-C7 bond connecting A and B THF rings accompanied by the oxidative removal of the terminal 2-hydroxypropyl moiety at the other end of the molecule (C22-C23 bond cleavage). Similarly, dilactone **13** (0.5 %), the *threo-cis-threo-trans-threo* isomer of **12,** originated from the analogous oxidative cleavage of both the C18-C19 bond, connecting D and E THF rings, and the oxidative cleavage of the C2-C3 bond. Conflicting NMR evidence prevented assignment of the configuration of the remaining tricyclic dilactone **14** (0.5%). Therefore, both *threo-cis-threo* and *threo-trans-threo* configurations are possible for this substance, according to two cleavage modes namely cleavage of C2-C3/C14-C15 or C10-C11/C22-C23 bond pairs, respectively.



Scheme 4. Minor polycyclic dilactones from the PCC-mediated degradation of **1** and relevant cleavage patterns (see arrows).

A mechanistic rationalization for the formation of spiroketals 9, 10 and dilactones 12-14. Isolation of the above products suggests new interesting oxidative pathways. A plausible mechanistic rationalisation for the formation of above spiroketal and dilactone substances that agrees with reported reactivity of PCC[1,2] and previously developed chemistry by our own group,[22] is given in schemes 5, and 7-9.

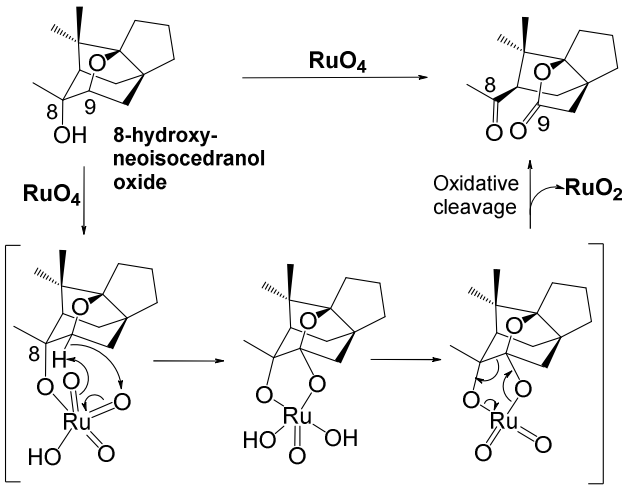
Initially, interaction of PCC with the C(2)-OH group gives rise to chromium ester **15** (Scheme 5). Thus, the oxo-chromium appendage tethered to C-2, in this intermediate, may attack the close-in-space C7-H bond, causing the closure of the spiroketal function of **5** (route a), with expulsion of a chromium species. Next, the oxidative cleavage of the C22-C23 bond in the latter generates the related terminal lactone **6.** However, an alternative route in which a cyclic chromium diester intermediate **16** is formed from **15** through the [3+2] addition of its O=Cr=O portion to the C7-H bond (route b), appears plausible.



Scheme 5. A mechanistic route explaining the formation of spiroketals **5** and **6**.

The preliminary formation of chromate ester **15** is a reasonable assumption since there is evidence of the very rapid formation of such esters by reaction of PCC with primary, secondary and tertiary alcohols.[34]
On the other hand, formation of chromium diester **16** from **15** is supported by a number of previously reported evidence. Attack of transition metal oxo-species such as RuO_4[35-38] and OsO_4[39-41] to C-H bonds of alkanes is well-known and has been suggested to proceed through [3+2] addition of a C-H bond across an O=M=O unit through a mechanism analogous to the one now widely accepted for alkene bis-hydroxylation. In addition, it has been reported that the RuO_4 oxidation of neoisocedrane oxide[42] (Scheme 6), a THF-containing sesquiterpene, proceeds much in the same way we hypothesize in the transformation of **15** to **16**, through the insertion of an oxoruthenium bond into the ether C-H bond of the THF ring, successive to the formation of a ruthenate ester, aspecies analogous to **15**. Conversion of **15** to **16** seems also plausible based on the similar oxidizing behaviour exhibited by RuO_4 and PCC towards **1**, recently disclosed in a study carried out in our group.[13,22]

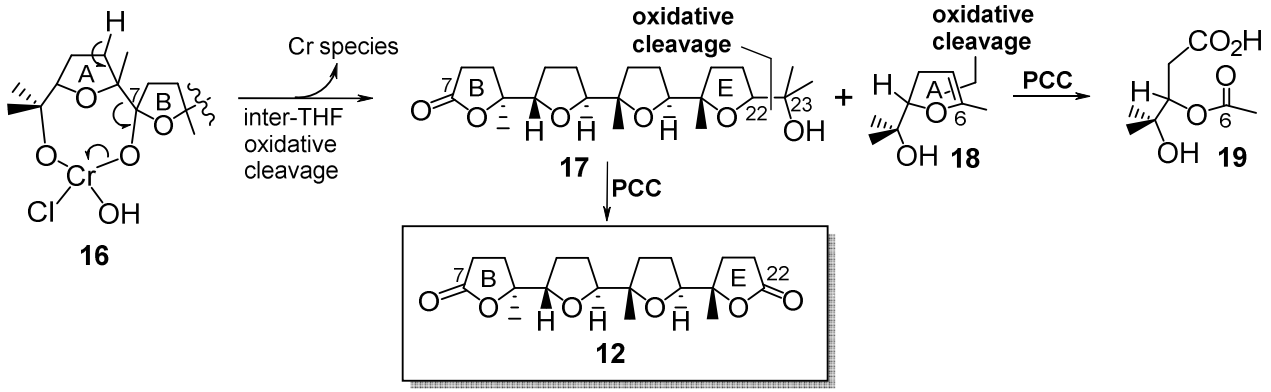
Formation of diester **16**, well explains the formation of compounds **9**, **10** and **12**, where the oxidation of the B-ring is required. In fact, **16** can be envisaged to evolve through two routes. In particular (Scheme 7), oxidative cleavage of the C6-C7 bond connecting A and B rings, would be responsible of the formation of intermediate mono-lactone **17** from which dilactone **12** would then be formed by cleavage of the C22-C23 bond. This route would concomitantly produce enolether **18** the C-C double bond of which would likely undergo oxidative cleavage to the dicarbonyl compound **19**, based on previous evidence on the reactivity of enolethers with PCC.[43-45] Although this compound could not be detected among the oxidation products of **1**, the benzoate of **18** (see later compound **32**, figure 3) has been isolated as a minor product when the dibenzoate of **1** was oxidised in the same conditions.[23] A chromium diester intermediate strictly similar to **16** has been postulated in the oxidative ring fission of 2,5-dialkylfuranes with PCC to give α,β-unsaturated 1,4-dicarbonyl compounds.[46]



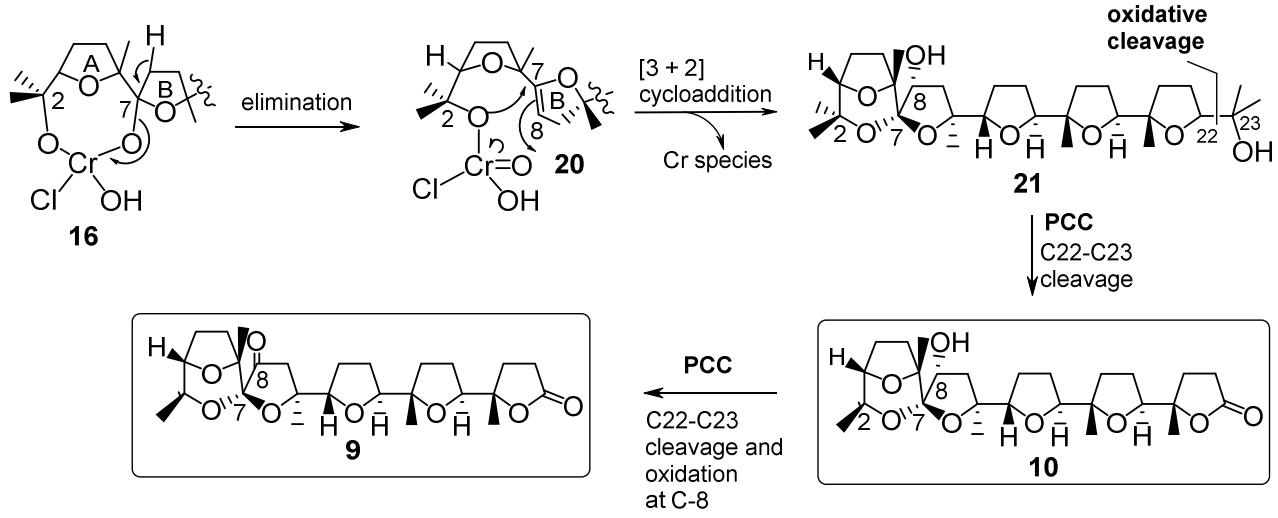
Scheme 6. Oxidative cleavage of 8-hydroxy-neoisocedranol oxide with RuO_4 based on literature data [42].

Alternatively, an elimination step in **16** can generate the ring-B enolether intermediate **20** (Scheme 8), where a chromium-containing appendage is still linked to C-2 and the carbon skeleton of **1** is preserved. This step sets the basis for the formation of the spiroketal moiety of **10** *via* a successive cycloaddition step, likely a [3+2] process involving the attack of the oxochromium appendage still tethered to C-2 on the □[7] double bond of **20**. The cleavage of the C22-C23 bond in the first-formed intermediate spiroketal species **21** then leads to

10. The above spiroketalization step also delivers the C-8 hydroxyl group. Finally, keto-spiroketal **9** originates from the corresponding alcohol **10** by further PPC oxidation at C-8.



Scheme 7. A mechanistic explanation for the formation of bis-lactone **12**.



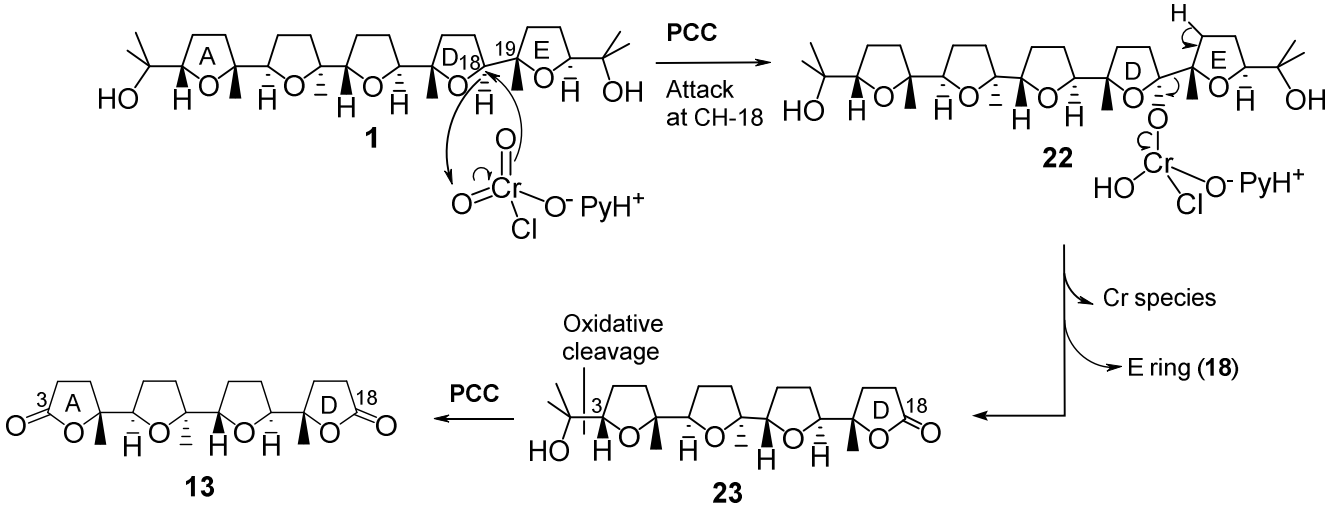
Scheme 8. Proposed mechanistic route for the formation of spiroketals **9** and**10**.

Conversion of **20** to **21** is a likely transformation because the PCC-mediated oxidative cyclization of bishomoallylic tertiary alcohols to THF-alcohols has previously been reported.[47-49] It is worth noting that such a cycloaddition step also explains the observed *cis* relationship between the ring-F spiroketal oxygen and the C-8 hydroxyl group (Figure 1).

Our hypothesis on the spiroketalization step involved into the conversion of **20** to **10** well agrees with the McDonald *et al.*[48] and Schlecht *et al.*[49] mechanistic proposals. This transformation is strongly reminiscent of the oxidative spirocyclization of cyclic enolethers mediated by rhenium (VII) oxides reported by Boyce and Kennedy[50] and would represent the first example of the PCC-induced formation of a cyclic spiroketal involving an enolether double bond. It is to be noted that this transformation involves the chromium ester of a tertiary alcohol (C2-OH) while the rhenium-mediated process is reported to induce the sole spiroketalization of primary alcohols. This transformation is certainly worth of further studies using *ad hoc* devised substrates.

Formation of dilactone **13**, the *cis-trans* isomer of **12**, would proceed in a way strictly analogous to that leading to **12**, by cleavage of C18-C19 and C2-C3 bonds, *via* intermediates **22** and **23** (Scheme9). However, in this case, due to the *threo-trans-threo* configuration of the bis-THF terminus (Figure 2), an intermolecular

attack of PCC to C18-H bond is to be invoked because a C23-tethered oxochromium appendage and the C18-H bond cannot be brought near in the space, as it happens in **15** (Scheme 5), This spatial arrangement also explains why no spiroketalization is observed at this terminus but only cleavage of the C22-C23 bond to give **2**.



Scheme 9. Proposed route for the formation of dilactone **13**.

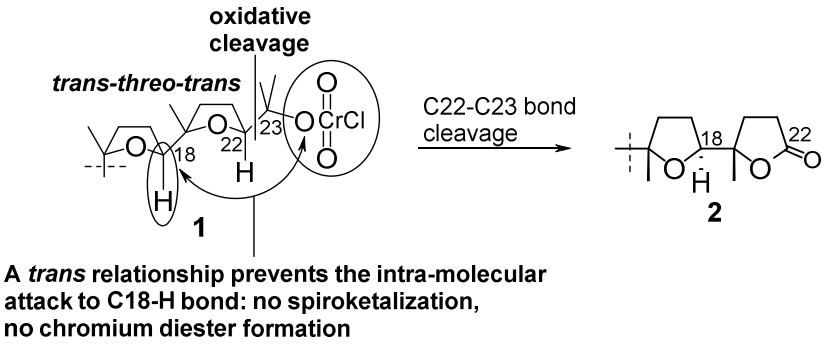
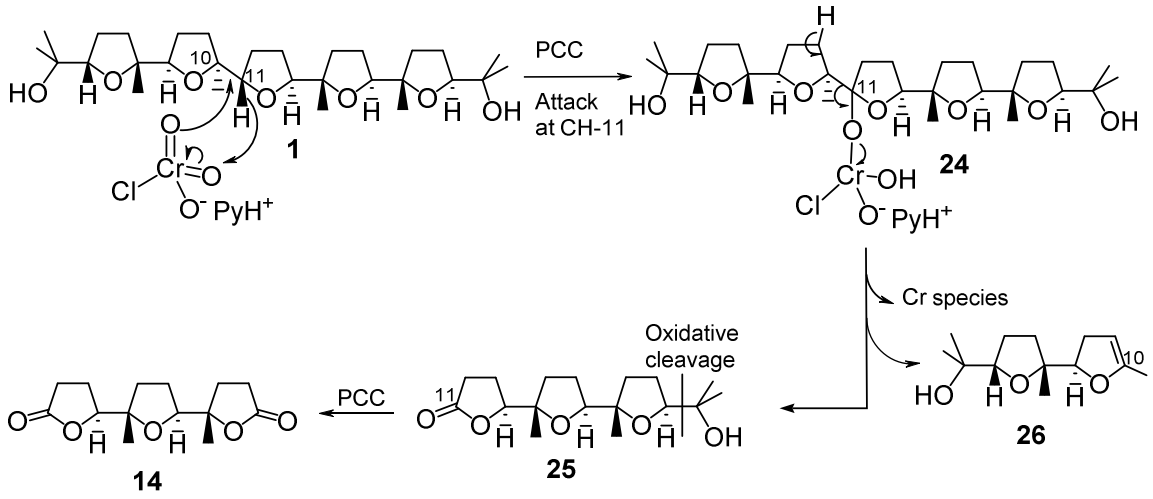


Figure 2. Fate of the postulated chromium ester formed at the terminal *trans-threo-trans* bis-THF portion of **1**.

Finally, formation of dilactone **14** from **1** is depicted in Scheme 10. It requires the cleavage of one of the bonds adjacent to the central THF ring (C10-C11 or C14-C15) to take place (the attack at the C11-H bond is shown in scheme 9). An inter-molecular attack of PCC is required in this case as well, to give the chromium ester intermediate **24** which then gives rise to bis-lactone **14** *via* mono-lactone **25**. A bis-THF enolether-containing species **26** would once again be produced in this step, the fate of which we were unable to follow further.

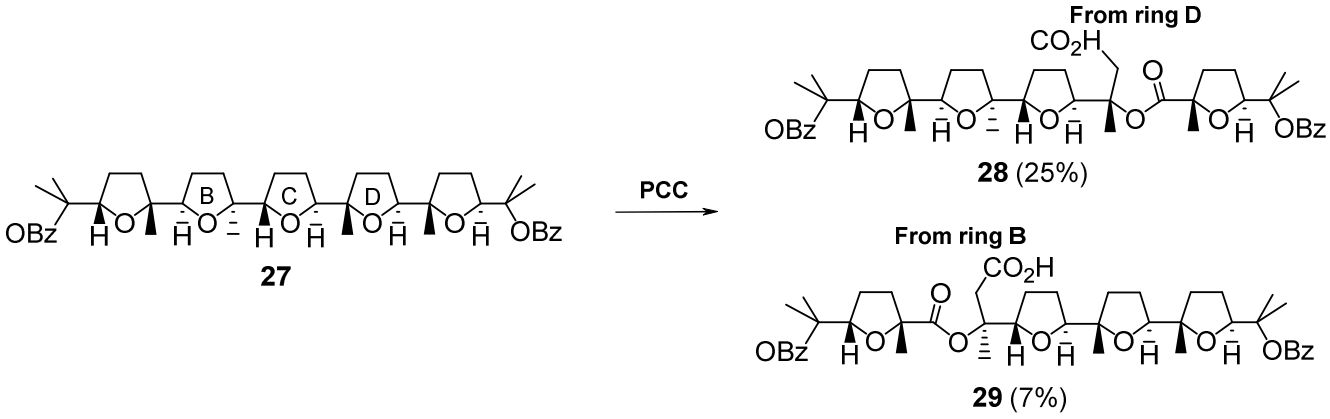
Summarising, the above results clearly established the ability of PCC to cleave inter-THF bonds in **1**.[23] The main oxidative routes, leading to γ-lactones **2**-**4**,[17,22] spiro-compounds **5** and **6** as well as minor C-8 oxygenated spiro-compounds **9** and **10**, and bis-lactone **12** (Schemes 1, 5, 7 and 8) proceed through the preliminary formation of chromium esters by interaction of PCC with the two hydroxyl groups of **1**. Secondary routes leading to truncated spirolactones **7** and **8** (Scheme 1), dilactones **13** (Scheme 9) and **14** (Scheme 10), likely proceed through the inter-molecular attack of PCC to suitable THF CH bonds followed by inter-THF C-C cleavage. There is evidence indicating the formation of cyclic enolethers. This also further supports our

recently formulated hypothesis on the involvement of an enolether species in the oxidative cleavage of trisubstituted THF rings with chlorochromatoperioadate (CCP), an oxidizing agent generated by reaction of PCC and periodic acid.[23]



Scheme 10. Proposed mechanism for the formation of dilactone **14**.

Minor oxidation products from the PCC-mediated oxidation of penta-THF dibenzoate 27. Previously, we have investigated the reactivity of compound **27**, the bis-benzoate of **1** (Scheme 11), in the same oxidative conditions used for the oxidation of **1**.[23] Because of the absence of free C-2 and C-23 hydroxyl groups in **1**, the main oxidative routes giving terminal lactones **2**-**4**, as well as spirocompounds **5**-**8** were depressed and the intermolecular attack of PCC to the internal THF rings in **1** was enhanced. This resulted in the formation of compounds **28** and **29** as the major products. We hypothesized that they could originate by the oxidative cleavage of ring-B or D enolethers.[23] In addition, ketol **30**, embodying a ring-B oxygenated moiety, lactone **31**, lacking one of the terminal rings of **27,** and fragment **32**, were also isolated as minor products. Formation of these compounds could be rationalised through involvement of ring-B or D enolethers, as well. Isolation of compounds **28**-**32** suggested the preferential attack of PCC to B and D rings in **27**. A reinvestigation of the oxidation of **27** with PCC,, in the previously tested conditions, has now led to the identification of further four minor products originating from the attack of the oxidant to the central C THF ring. Their formation has been explained through mechanistic paths in line with those formulated for all the other reaction products. In particular, the two isomeric, small-sized, lactones **33** and **34** (major isomer 4%; minor isomer 2%) and the two isomeric unsaturated aldehydes **35** and **36** (1% each), were isolated.



Scheme 11. Major products from the oxidation of penta-THF dibenzoate **31**.

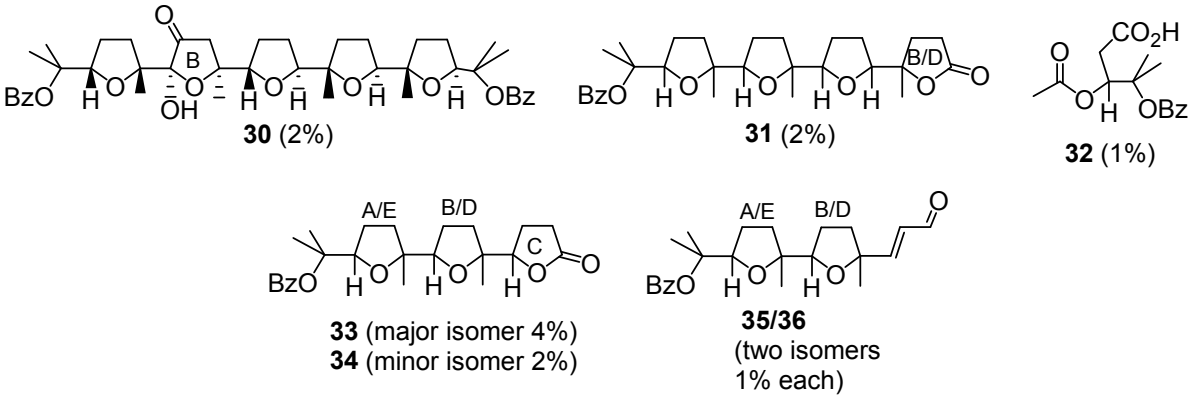
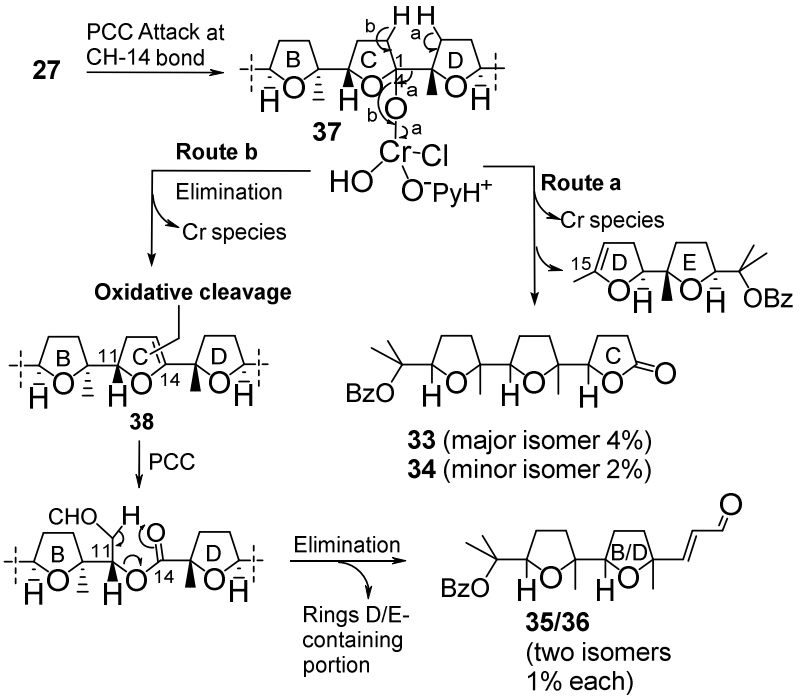


Figure 3. Minor products from the oxidation of penta-THF dibenzoate **23** with PCC.

Formation of degraded compounds **33-36** can be rationalized through attack of PCC to C11-H or C14-H in the central THF ring (Scheme 12), according to mechanistic routes above depicted for the oxidation of **1** (Schemes 9 and 10). When reasoning for the attack at C14-H, lactones **33** and **34** would derive from the monoester intermediate **37** by oxidative cleavage of C14-C15 bond (route a). An alternative path (route b) would lead to the ring-C enolether **38**, by elimination of a chromium species. Oxidative cleavage of the enolether double bond in the latter, followed by the further elimination of the rings D/E-containing portion of the molecule, would give rise to the conjugated aldehydes **35** and **36**.

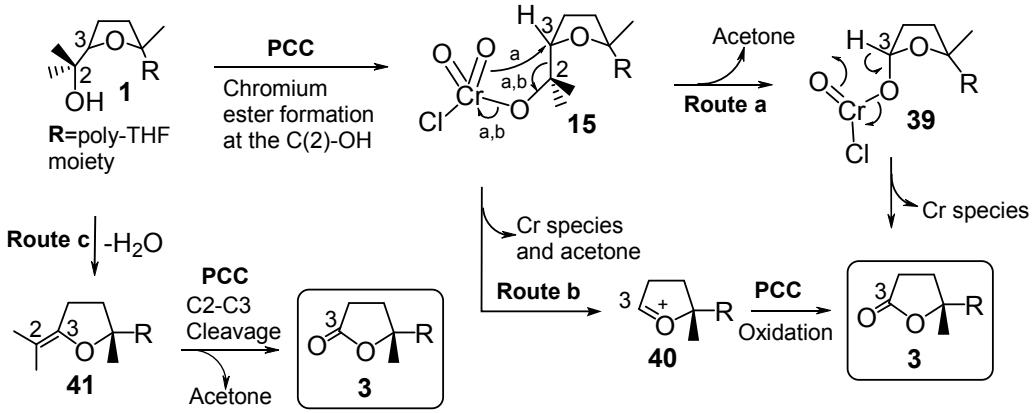


Scheme 12. Formation of **33-36** from **27**.

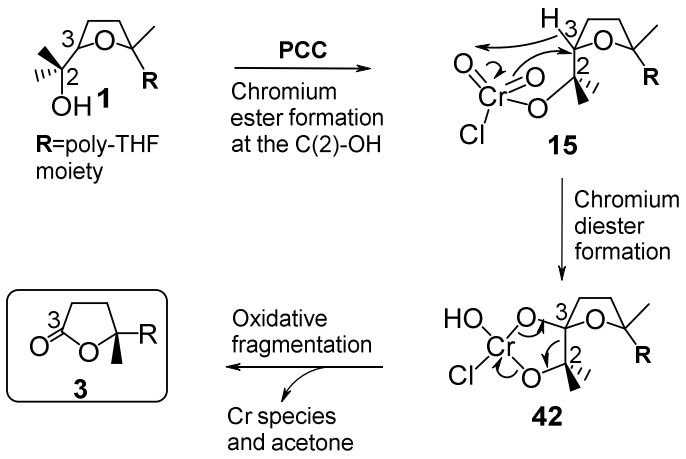
A new proposed mechanism for the oxidative cleavage of α-hydroxy-THF compounds. Conversion of 1 to 2-4. The PCC-mediated oxidative cleavage of α-hydroxy mono- and poly-THF compounds to γ-lactones (see for example conversion of **1** to **2**-**4** or **5** to **6** in Scheme 1) is a well-documented process[25-29] interesting both from a mechanistic and applicative point of view. No definitive evidence on the real path of this transformation has been provided to date although plausible speculative reasoning have been put forward.[17,25-29] In the light of the above collected evidence a comment to this transformation, with reference to THF bearing α-tertiary alcoholic moieties, seems appropriate. When reasoning for example for the transformation of **1** to **3** (Scheme 1), a summary of the reported routes, explaining the oxidative cleavage of the C2-C3 bond, is shown in Scheme 13.

In particular, the great part of the reported hypotheses supposes a preliminary coordination of PCC to the alcohol group α to the THF ring. In accord with the route proposed by Stark et al.[25] for the strictly related oxidative cleavage of THF and THP alcohols to γ- and δ-lactones, the C-2 tethered oxochromium appendage in the first-formed species **15** may attack the C-3 carbon though route a, with formation of a C-3 chromium ester intermediate **39** that, as such or in a different oxidation state, would generate the lactone function in **3**. Alternatively, a cation species **40**[17,25] could be formed (route b) that is then further oxidised by PCC to give **3**. Another reported route (route c)[28] supposes the involvement of an enolether species such as **41**, formed by dehydration, that is then cleaved by PCC. However, such a type of substance could not be detected among the reaction products, as the authors pointed out.[28] In line with our reasoning on the conversion of **15** to **16** shown in Scheme 5, we believe that a fourth plausible path (Scheme 14) can be proposed where the C3-H bond is attacked by the close-in-space C-2 tethered oxidant, to give the cyclic chromium diester **30**. Successive oxidative fragmentation of this intermediate, would proceed in the usual manner with expulsion of acetone, generating the lactone function of **3**. Note that this route would compete with the one where the C7-H is attacked by the same C-2 oxochromium portion to give **16**, as shown in Scheme 5. Cyclic esters such as **42** are thought to be involved into the oxidative cleavage of alkenes or vicinal diols with related oxo-species RuO_4,

OsO_4, RuO_4^- and MnO_4^-. Importantly, our path is strictly similar to the proposed route for the oxidative cleavage observed for 8-hydroxy-neoisocedranol oxide with RuO_4 shown above in Scheme 6,[42,3,13,] which we also postulated to work in the ruthenium tetroxide catalyzed oxidative cleavage of strictly related poly-THF spiroketal compounds.[13] On this ground it seems conceivable that this route could also work in the oxidative cleavage of related α-hydroxy-THF substances studied by others.[25-29]



Scheme 13. Oxidative cleavage of the α-hydroxy-THF portion of **1** according to previously formulated mechanistic hypotheses.



Scheme 14. Our proposed route for the oxidative cleavage of the α-hydroxy-THF portion in **1**.

Conclusions

The data collected in the present study expand our knowledge on the oxidative behaviour of PCC with poly-THF compounds under classical conditions and may help to understand the reactivity of PCC with simpler ether compounds. Penta-THF **1** revealed itself as a good model compound to study the action of PCC on adjacently linked poly-THF compounds. Novel oxidative pathways leading to degradation, or oxidative modification, of the poly-THF skeleton, with formation of new types of poly-THF compounds, have been disclosed. Plausible hypotheses, consistent with the known reactivity of PCC, have been presented to explain the formation of all isolated substances. In particular, attack of the oxidant at the various THF C-H bonds, either in an intra- or inter-molecular way, is thought to be the first event, which

leads to formation of a chromium ester intermediate. The main products originate from the first-formed chromium ester species with the alcohol functions in **1**. Inter-THF bond cleavage, to give small-sized dilactones, takes place in a little extent by intra-molecular attack of PCC to THF rings. Isolation of minor C-8 oxygenated spiroketal compounds strongly suggests that a cyclic ring-B enolether is involved in their formation. We believe that further experimental work on the chromium-mediated spiroketalization of cyclic enolethers, including α-tethered tertiary alcohol portions in their structure, is certainly desirable. Oxidation of dibenzoate **27** led to degraded compounds the formation of which is explained through the intervention of ring-C enolethers in this case as well. Additional support to the previously observed similarity of the chemical oxidative behaviour of PCC and RuO_4 towards THF-containing substances,[13] has been provided. Further clarification of this issue could come from theoretical studies.

Experimental Section

General. All reagents were purchased at the highest commercial quality and used without further purification. 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 work-up. HPLC separations were carried out on a Varian 2510 apparatus equipped with a Waters R403 dual cell differential refractometer using Phenomenex 250 x 10 mm and 250 x 4.6 mm (both 5μ) and LiChrosorb RP-18 250 x 4.0 mm columns. NMR experiments were performed on Varian Unity Inova 700, Varian Unity-Inova 500, Varian Mercury Plus 400, Gemini 200 spectrometers in $CDCl_3$. Proton chemical shifts were referenced to the residual $CHCl_3$ signal (7.26 ppm). ^{13}C-NMR chemical shifts were referenced to the solvent (77.0 ppm). *J* values are given in Hz. Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra were recorded on a Jasco FT-IR 430 spectrophotometer. The High Resolution MS were recorded on a Bruker APEX II FT-ICR mass spectrometer using electron spray ionization (ESI) technique. For all the reported products the numbering previously given[17] for the penta-THF **1** is used.

Penta-THF 1 and its oxidation with PCC/AcOH. Isolation of minor products 9, 10 and 12-14. Penta-THF **1** was synthesized as previously described.[17] To a solution of **1** (332 mg, 0.63 mmol) in CH_2Cl_2 (5 mL) was added PCC (5 equiv. 3.16 mmol, 682 mg) and AcOH (70 equiv., 2.5 mL) and the resulting heterogeneous mixture was stirred at room temperature for 6h. A saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2. The combined extracts were dried and evaporated *in vacuo* to give a yellow oil. Filtration on a silica gel pad (eluent $CHCl_3$-MeOH, 9:1) afforded a colourless oil (310 mg) that was separated by HPLC (250x10 mm column; flow: 2.5 mL/min; eluent: hexane-EtOAc, 65:35) to give spirolactone **7** (2.5 mg, 1%, t_R 13.5 min), spirolactone **8** (1.9 mg, 1%, t_R 18.5 min), spiroketone **9** (3.1 mg, 1%, t_R 15.0 min), spiroalcohol **10** (1.6 mg, 0.5%, t_R 17.5 min) and bis-lactone **12** (2.1 mg, 1 %, t_R 41.0 min). The fraction eluted in the range 26-38 min contained a mixture of bis-lactones **13** and **14**. A further HPLC run of this fraction (eluent: hexane-EtOAc, 3:7) gave *ca.* 80% pure **13** (t_R 17.0 min) and **14** (t_R 15.0 min). Final purification of these substances was carried out by reversed-phase HPLC (250 x 4.6 mm column; flow: 1.0 mL/min; **13**: eluent CH_3CN/H_2O, 6:4, t_R 4.5 min; **14**: eluent CH_3CN/H_2O, 7:3, t_R 3.0 min) to give **13** (1.0 mg, 0.5%) and **14** (0.8 mg, 0.5%).

9. Amorphous solid; IR (neat) ν_{max} 1763, 1699, 1045 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) selected values δ 3.91 (1H, d, *J* 7.0), 3.87-3.79 (3H, m), 2.88 (1H, ddd, *J* 13.0, 9.7, 5.4), 2.86 (1H, d, *J* 17.6, H_a-9), 2.76 (1H, ddd, *J* 17.6, 10.6, 9.4, H_a-21), 2.45 (1H, ddd, *J* 17.6, 10.3, 3.3, H_b-9), 2.36 (1H, d, *J* 7.6, H_b-9) 2.35 (1H, m, partially

overlapped to the H_b-9 signal), 2.14-2.00 (3H, overlapped multiplets), 2.00-1.82 (7H, overlapped multiplets), 1.60 (1H, ddd, *J* 12.1, 7.8, 4.8), 1.40 (1H, ddd, *J* 12.8, 12.8, 4.2), 1.52, 1.35, 1.32, 1.21, 1.06, 1.04 (3H each, s's, 6xMe); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 208.9, 178.0, 100.9, 86.3, 85.8, 85.3, 84.9, 83.7, 82.6, 81.3, 78.7, 76.0, 44.9, 34.4, 32.4, 30.3, 30.0, 27.6, 26.7, 26.5, 26.2, 26.1, 25.6, 25.0, 23.9, 23.4, 21.2; HRMS (ESI) *m/z* calcd for $C_{27}H_{40}NaO_8$ $[M+Na]^+$ 515.2621, found 515.2630.

10. Amorphous solid; IR (neat) ν_{max} 3398 (br), 1763 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) selected values δ 4.09 (1H, dt, *J* 11.1, 8.7, 8.7), 3.90 (1H, d, *J* 6.9), 3.83 (1H, dd, *J* 7.3, 7.3), 3.75 (1H, m) 3.57 (1H, m), 2.77 (1H, dt, *J* 16.9, 9.3, 9.3), 1.54, 1.33, 1.30, 1.26, 1.09, 1.02 (3H each, s's, 6xMe); HRMS (ESI) *m/z* calcd for $C_{27}H_{42}NaO_8$ $[M+Na]^+$ 517.2777, found 517.2789.

12. Oil; IR (neat) ν_{max} 1769 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.88-3.81 (2H, m), 3.79 (1H, dd, *J* 9.6, 5.5), 2.83-2.70 (2H, m), 2.52-2.32 (4H, overlapped multiplets), 2.09-1.76 (9H, overlapped multiplets), 1.68-1.60 (1H, m), 1.33 (6H, s, 2 x Me), 1.05 (3H, s, Me); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 177.9, 177.6, 86.3, 86.1, 85.74, 85.68, 85.3, 84.7, 34.5, 32.6, 32.3, 29.9, 29.8, 27.2, 26.9, 26.5, 23.9, 23.5, 23.0; HRMS (ESI) *m/z* calcd for $C_{19}H_{29}O_6$ $[M+H]^+$ 353.1964, found 353.1948.

13. Oil; IR (neat) ν_{max} 1769 cm^{-1}; ^{1}H-NMR 400 MHz, $CDCl_3$) selected values δ 3.94 (1H, dd, *J* 7.4, 7.4), 3.84 (1H, dd, *J* 7.5, 7.5), 3.72 (1H, dd, *J* 9.7, 4.4), 2.82-2.67 (2H, m), 2.54 (1H, bt, *J* 12.7), 2.48-2.37 (3H, overlapped multiplets), 2.10 (1H, m), 1.35, 1.31, 1.09 (3H each, s's, 3 x Me); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 178.1, 177.7, 86.7, 85.7, 84.89, 84.81, 84.0, 83.7, 34.8, 32.6, 32.2, 30.04, 30.00, 27.1, 26.7, 26.6, 24.6, 24.0, 23.3; HRMS (ESI) *m/z* calcd for $C_{19}H_{29}O_6$ $[M+H]^+$ 353.1964, found 353.1951.

14. Oil; IR (neat) ν_{max} 1762 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.36 (1H, dd, *J* 6.8, 6.8), 3.90 (1H, dd, *J* 7.8, 7.8), 2.74-1.87 (11H, overlapped multiplets), 1.80-1.72 (1H, m), 1.32 (3H, s, Me), 1.15 (3H, s, Me); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 177.7, 177.3, 86.9, 85.8, 85.3, 84.5, 34.0, 32.4, 29.9, 28.6, 26.1, 23.8, 23.0, 22.8; HRMS (ESI) *m/z* calcd for $C_{14}H_{21}O_5$ $[M+H]^+$ 269.1389, found 269.1380.

Borohydride reduction of 9. To a solution of **9** (3.0 mg, 0.0061 mmol) in anhydrous ethanol (1 mL) was added $NaBH_4$ (a tip of spatula) at room temperature under stirring. After 1h the mixture was diluted with ethanol (1 mL) and AcOH (two drops) was added. The mixture was filtered and the solid was thoroughly washed with ethanol. The organic phase was dried (Na_2SO_4) and taken to dryness under reduced pressure to give a colourless oil (3 mg). HPLC separation (250 x 4.6 mm column; flow: 1.0 mL/min; hexane/EtOAc, 1:1) gave pure samples of **10** (0.3 mg, 10%, t_R 6.8 min) and **11** (2.5 mg, 75%, t_R 35.5 min).

11. Oil;. IR (neat) ν_{max} -3400 (br) cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) selected values δ 4.11 (1H, q, *J* 9.1), 3.90 (1H, bd *J* 7.5), 3.78 (1H), 3.72-3.80 (2H, m), 3.65 (2H, t *J* 5.4), 3.60 (1H, dd *J* 9.1, 4.8), 2.57 (1H, ddd, *J* 12.9, 9.9, 4.7), 2.48 (1H, m), 2.14 (1H, bddd, *J* 10.0, 10.0, 10.0), 2.00 (1H, ddd, *J* 13.0, 9.5, 5.4), 1.42 (1H, ddd, *J* 12.6, 12.6, 4.8), 1.54, 1.52, 1.31, 1.25, 1.085, 1.080, 1.077 (3H each, s's, 6xMe); ^{13}C NMR ($CDCl_3$, data from 500 MHz HMBC) δ 104.1, 86.1, 85.7, 84.7, 84.3, 81.9, 81.7, 80.0, 75.4, 72.7, 72.1, 63.6, 44.2, 37.2 (two carbons), 34.5, 31.2, 27.0 (two carbons), 26.7, 26.6, 26.3, 26.0, 25.0, 23.9, 21.4, 21.2; HRMS (ESI) *m/z* calcd for $C_{27}H_{46}NaO_8$ $[M+Na]^+$ 521.3090, found 521.3075.

Oxidation of 27 with PCC/AcOH. Isolation of minor products 33-36. Penta-THF dibenzoate **27** was synthesized as previously described.[23] Oxidation of **27** (365 mg, 0.50 mmol) with PCC as reported[23] followed by filtration of the crude on a silica gel pad (eluent $CHCl_3$-MeOH, 9:1) gave an oily product (350 mg). Separation by HPLC (250x10 mm column; flow: 2.5 mL/min; eluent: hexane-EtOAc, 75:25) gave still impure compounds **33-36** along with previously isolated compounds **28-32**. Analytical HPLC (250 x 4.6 mm column; flow: 1.0 mL/min; 3 mg/injection, hexane/EtOAc, 75:25) afforded lactones **33** (t_R 18.0 min) and **34** (t_R 13.0 min). Pure aldehydes **35**

(1.2 mg, 1%, t_R 13.8 min) and **36** (1.2 mg, 1%, t_R 10.0 min) were obtained by HPLC on the same column by using hexane/EtOAc, 85:15. A further reversed-phase HPLC run (250 x 4.0 mm column; flow: 1.0 mL/min; 2 mg/injection) was required to obtain pure **33** (MeCN/H_2O, 8:2, 5.0 mg, 4%, t_R 5.0 min) and **34** (MeCN/H_2O, 85:15, 2.5 mg, 2%, t_R 4.5 min).

33 (major isomer). Oil; IR (neat): ν_{max} 1775, 1712, 1288, 713 cm^{-1}**;** ^{1}H-NMR: (500 MHz, $CDCl_3$) selected values δ 7.96 (2H, dd, *J* 8.0, 1.0, phenyl *orto* protons), 7.52 (H, dddd, *J* 7.4, 7.4, 1.2, 1.2, phenyl *para* proton), 7.42 (2H, bt, *J* 7.8, phenyl *meta* protons), 4.36 (1H, dd, *J* 7.9, 6.1), 4.19 (1H, dd, *J* 7.0, 7.0), 3.95 (1H, dd, *J* 9.2, 6.1), 2.56 (1H, ddd, *J* 17.7, 10.1, 6.3), 2.40 (1H, ddd, *J* 17.5, 10.3, 7.1), 2.32-2.24 (1H, m), 2.20-2.09 (2H, overlapped multiplets), 2.08-2.0 (1H, m), 1.95-1.96 (2H, overlapped multiplets), 1.84-1.75 (1H, m), 1.61, 1.59, 1.20, 1.19 (3H each, s's, 4xMe); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 177.7, 165.7, 132.5, 131.8, 129.4 (two carbons), 128.2 (two carbons), 84.4, 84.3, 83.8 (two carbons), 83.1, 83.0, 34.3, 32.3, 28.7, 27.6, 26.6, 23.1 (two carbons), 22.9, 22.6, 21.5; HRMS (ESI) *m/z* calcd for $C_{24}H_{32}NaO_6$ $[M+Na]^+$ 439.2097, found 439.2106.

34 (minor isomer). Oil; IR (neat): ν_{max} 1776, 1712, 1288, 714 cm^{-1}**;** ^{1}H-NMR: (400 MHz, $CDCl_3$) selected values δ 7.98 (2H, bd, *J* 8.2, phenyl *orto* protons), 7.52 (H, bt, *J* 7.0, phenyl *para* proton), 7.41 (2H, bt, *J* 7.5, phenyl *meta* protons), 4.38 (1H, dd, *J* 7.4, 4.8), 4.19 (1H, dd, *J* 9.3, 5.6), 3.85 (1H, dd, *J* 9.5, 5.8), 2.65 (1H, ddd, *J* 17.2, 9.8, 6.8), 2.45 (1H, ddd, *J* 17.1, 10.6, 6.3), 1.60 (6H s, 2xMe), 1.19, 1.13 (3H each, s's, 2xMe); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 177.7 165.7, 132.4, 129.4 (two carbons), 128.1 (two carbons), 87.0, 85.9, 84.8, 83.6, 83.5, 83.3, 34.6, 34.1, 28.6, 26.9, 26.5, 24.5, 23.5, 22.9, 22.8, 21.6; HRMS (ESI) *m/z* calcd for $C_{24}H_{32}NaO_6$ $[M+Na]^+$ 439.2097, found 439.2100.

35. Oil; IR (neat): ν_{max} 1712, 1288, 712 cm^{-1}**;** ^{1}H-NMR: (500 MHz, $CDCl_3$) selected values δ 9.41 (1H, d, *J* 7.8), 7.98 (2H, d, *J* 8.0, phenyl *orto* protons), 7.52 (H, bt, *J* 7.8, phenyl *para* proton), 7.40 (2H, bt, *J* 8.0, phenyl *meta* protons), 6.88 (1H, d, *J* 15.6), 6.17 (1H, dd, *J* 15.6, 7.8), 4.21 (1H, dd, *J* 6.8, 6.8), 4.06 (1H, dd, *J* 6.8, 6.8), 1.62, 1.61, 1.37, 1.22 (3H each, s's, 4xMe); HRMS (ESI) *m/z* calcd for $C_{23}H_{30}NaO_5$ $[M+Na]^+$ 409.1991, found 409.1996.

36. Oil; IR (neat): ν_{max} 1712, 1288, 712 cm^{-1}**;** ^{1}H-NMR: (500 MHz, $CDCl_3$) selected values δ δ 9.58 (1H, d, *J* 7.9), 7.98 (2H, d, *J* 8.2, phenyl *orto* protons), 7.52 (H, bt, *J* 7.4, phenyl *para* proton), 7.41 (2H, bt, *J* 8.0, phenyl *meta* protons), 6.84 (1H, d, *J* 15.6), 6.27 (1H, dd, *J* 15.6, 7.9), 4.23 (1H, dd, *J* 9.6, 5.6), 3.94 (1H, dd, *J* 6.0, 6.0), 1.61 (6H, s, 2xMe), 1.42, 1.18 (3H each, s's, 2xMe); HRMS (ESI) *m/z* calcd for $C_{23}H_{30}NaO_5$ $[M+Na]^+$ 409.1991, found 409.1990.

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