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Communication

A Novel PCC-Catalyzed Process Involving the Oxidative Cleavage of an α-Bromomethyl-tetrahydrofuran Bond. Synthesis of (2*S*,3*R*)-2-{(*R*)-Bromo[(2*R*,3*R*,5*S*,6*R*)-3,5-dibromo-6-ethyltetrahydro-2*H*-pyran-2-yl]methyl}-5-oxotetrahydrofuran-3-yl Benzoate

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Abstract: In this note, we report the discovery of a novel pyridinium chlorochroamte-catalyzed process in which an α-bromomethyl-tetrahydrofuran bond was oxidatively cleaved to give a γ-lactone functionality. The title compound was synthesized from a C15 polybrominated acetogenin compound, isolated from the marine sponge *Mycale rotalis*, by benzoylation followed by pyridinium chlorochromate-catalyzed oxidation. This new degraded derivative was fully characterized by ^{1}H-NMR, ^{13}C-NMR, FTIR (Fourier transform infrared), EIMS (Electron impact mass spectrometry) and HRESIMS (High-resolution electrospray ionisation mass spectrometry).

Keywords: pyridinium chlorochromate; α-bromomethyl-tetrahydrofuran; oxidative cleavage; γ-lactone

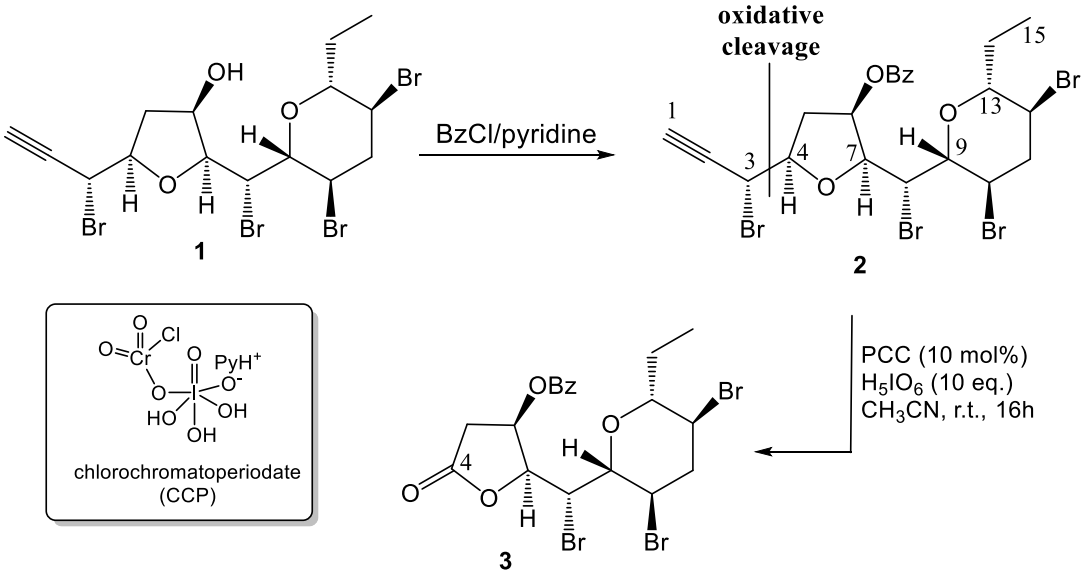
1. Introduction

Oxidation methods, mediated or catalyzed by transition metal oxo-species, are a class of processes of pivotal importance in organic synthesis [1–4]. Pyridinium chlorochroamte (PCC) is a well known oxidizing reagent. Although it is mostly used in the oxidation of primary and secondary alcohols to aldehydes and ketones, respectively, it has also been employed in a number of other processes [5], and recently, we [6–9] and others [10–14] have disclosed its ability to catalyze new synthetically useful reactions. We were now interested in testing some oxidative methods previously developed in our laboratories [8,15–17] on a number of structurally diverse molecular frameworks in order to access a selection of variously functionalized substances for structure-activity relationship studies [18]. During these studies, we came across a novel PCC-catalyzed process featuring the oxidative cleavage of an α-bromomethyl-tetrahydrofuran bond to give a γ-lactone functionality. In particular, we report here the synthesis of the title compound through the oxidative degradation of a polybrominated acetogenin substance previously isolated in our laboratories from the marine sponge *Mycale rotalis* [19].

2. Results and Discussion

The starting compound **1** (Scheme 1) was benzoylated with excess BzCl in pyridine to give benzoate **2**. The next oxidation step was carried out by application of a slightly modified oxidative procedure previously developed in our laboratories [8]. In particular, compound **2** was oxidized with a catalytic amount (10 mol %) of PCC in the presence of excess periodic acid (H_5IO_6, 10 equiv.), as the primary oxidant, to give compound **3** in 50% isolated yield and in a reproducible manner. Contrary to what we observed in our previous conditions [8], the process could proceed at a reasonable rate only

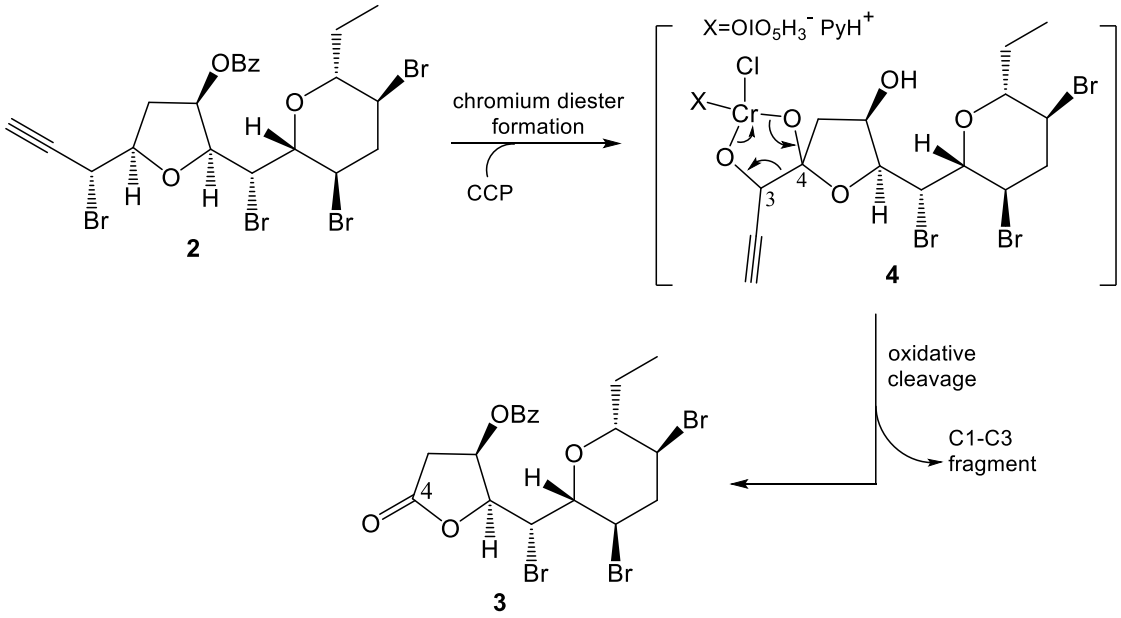
at room temperature. Spectral data for **3** (see Supplementary Material) were in full agreement with the reported structure. In particular, FT-IR (υ_{max} 1795 cm^{-1}) (see Supplementary) and ^{13}C-NMR (δ 171.9 ppm) (see Supplementary) data pointed to the presence of a γ-lactone ring in **3**. In addition to data from NMR spectra (for the ^{1}H-NMR see Supplementary), the structure of **3** was well secured by HRESIMS (see Supplementary) and EIMS (see Supplementary) data. Particularly informative was the EIMS spectrum (GC-MS mode) of **3** recorded with a high sample pressure [20]. It showed a low-intensity, four-peak MH^+ at m/z 567/569/571/573, derived from the ion-molecule reaction typical of ethers [20], indicating the presence of three bromine atoms in the molecule, as well as fragmentation peaks relevant to three stepwise HBr losses, while suggesting the lack of the terminal bromoalkyne moiety. FTIR data well supported the absence of the alkyne function while offering clear evidence for a γ-lactone function.



Scheme 1. Synthesis of (2*S*,3*R*)-2-{(*R*)-Bromo[(2*R*,3*R*,5*S*,6*R*)-3,5-dibromo-6-ethyltetrahydro-2*H*-pyran-2-yl]methyl}-5-oxotetrahydrofuran-3-yl Benzoate (**3**).

According to literature precedents [7,8,21], it is presumable that the active oxidizing species could be chlorochromatoperiodate (CCP, Scheme 1) formed by combination of PCC and periodic acid with water loss. In particular, the α-bromomethyl-tetrahydrofuran bond in the benzoylated species **2** (Scheme 1) underwent a novel type of oxidative cleavage to give the γ-lactone ring present in the final product **3**, with the elimination of the three-carbon (C1–C3), bromoalkyne fragment. This process is strongly reminiscent of the pyridinium chlorochromate-mediated oxidative cleavage of α-hydroxymethyl-tetrahydrofurans to γ-lactones previously studied in our group [9,22].

The mechanism of this new process is unknown, but the involvement of a cyclic chlorochromatoperiodate diester (**4**, Scheme 2) can be hypothesized in agreement with literature precedents [7,8,21] and recent results disclosed by our studies [9].



Scheme 2. Proposed mechanism for the formation of lactone **3**.

3. Materials and Methods

3.1. General Information

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 KGaA, Darmstadt, Germany). NMR experiments were performed with a Varian Unity Inova spectrometer (Varian Inc., Palo Alto, CA, USA) at 400 MHz 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. Coupling constants are given in Hertz. IR spectra were recorded neat with a Jasco FT-IR 430 spectrophotometer (JASCO, GmbH, Germany) and are reported in cm^{-1}. HRMS spectra were recorded by infusion on Thermo LTQ Orbitrap XL mass spectrometer (Thermo Fisher Scientific, Waltham, MA, USA) with an Electrospray source in the positive mode using MeOH as solvent. Low-resolution EI-MS spectrum of **3** was obtained operating at 70 eV on a GCMS-QP5050A (Shimadzu Corporation, Kyoto, Japan).

*3.2. Synthesis of (2S,3R,5R)-2-{(R)-Bromo[(2R,3R,5S,6R)-3,5-dibromo-6-ethyltetrahydro-2H-pyran-2-yl]methyl}-5-[(R)-1-bromoprop-2-yn-1-yl]tetrahydrofuran-3-yl Benzoate (**2**)*

Benzoyl chloride (10 equiv., 0.65 mmol, 75 µL) was added to **1** (36.7 mg, 0.065 mmol) dissolved in pyridine (400 µL), and the mixture was stirred at room temperature for 16 h. Methanol (0.5 mL) was added, and the mixture was stirred for 15 min. and then taken to dryness to give an oily product. Purification by preparative TLC (silica, hexane/EtOAc, 8:2, R_f = 0.54) afforded the benzoyl-derivative **2** (16.2 mg, 37%) as a clear oil.

2: ^{1}H-NMR (400 MHz, $CDCl_3$) (see Supplementary), δ (ppm): 8.07 (2H, d, *J* = 8.1), 7.60 (1H, t, *J* = 7.6), 7.45, (2H, t, *J* = 7.5), 5.43 (1H, bdd, *J* = 5.4, 2.8), 4.85 (1H, bdd, *J* = 9.4, 1.1), 4.64 (1H, dd, *J* = 5.9, 2.3), 4.40 (1H, ddd, *J* = 8.8, 5.4, 5.4), 4.35 (1H, dd, *J* = 9.5, 3.1), 4.16 (1H, m), 3.71 (1H, ddd, *J* = 11.8, 11.8, 4.1), 3.43–3.32 (2H, m), 2.91 (1H, ddd, *J* = 13.0, 4.0, 4.0), 2.77 (1H, ddd, *J* = 15.2, 8.7, 6.0), 2.47 (1H, dd, *J* = 15.4, 4.9), 2.36–2.25 (2H, m), 2.04 (1H, m), 1.56 (1H, m), 0.97 (3H, t, *J* = 7.3); ^{13}C-NMR (101 MHz, $CDCl_3$) (see Supplementary), δ (ppm) 165.6, 133.7, 129.9, 129.1, 128.5, 84.2, 83.7, 80.2, 79.5, 79.1, 76.8, 73.0, 51.9, 47.2, 46.5, 44.9, 37.2, 36.6, 25.8, 9.6; ESIMS *m/z*: $[M + Na]^+$ 691/693/695/697/699.

*3.3. (2S,3R)-2-{(R)-Bromo[(2R,3R,5S,6R)-3,5-dibromo-6-ethyltetrahydro-2H-pyran-2-yl]methyl}-5-oxotetrahydrofuran-3-yl Benzoate (**3**)*

PCC (10 mol %, 240 μL of a 0.01 M stock solution in acetonitrile) was added at room temperature to a vigorously stirred suspension of H_5IO_6 (10 equiv., 0.24 mmol, 54.2 mg) in acetonitrile (100 μL). After 5 min., compound **2** (16.0 mg, 0.024 mmol) dissolved in acetonitrile (100 μL + 60 μL rinse) was added. After 16 h, CH_2Cl_2 (500 μL) was added followed by ethanol (100 μL), and the mixture was taken to dryness. Preparative TLC on silica gel (hexane–EtOAc, 8:2, R_f = 0.40) gave pure **3** (7.3 mg, 50%) as an oil.

3: IR (neat): υ_{max} 1795, 1721, 1265 cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ (ppm): 8.05 (2H, d, *J* = 7.6), 7.64 (1H, t, *J* = 7.6), 7.48, (2H, t, *J* = 7.6), 5.67 (1H, bdd, *J* = 4.4, 4.4), 4.98 (1H, dd, *J* = 9.7, 3.2), 4.90 (1H, dd, *J* = 9.7, 1.6), 4.17 (1H, m), 3.73 (1H, m), 3.45–3.33 (2H, m), 3.07 (1H, dd, *J* = 18.2, 5.1), 2.93 (1H, ddd, *J* = 12.9, 4.5, 4.5), 2.84 (1H, d, *J* = 18.2), 2.31 (1H, ddd, *J* = 12.7, 12.7, 12.7), 2.05 (1H, m), 1.60 (1H, m), 0.99 (3H, t, *J* = 7.4); ^{13}C-NMR ($CDCl_3$), δ (ppm): 171.9, 165.3, 134.3, 130.0, 128.7, 128.1, 83.8, 83.4, 79.3, 70.2, 50.2, 46.7, 46.0, 44.7, 38.0, 25.7, 9.6; EIMS *m*/*z*: 567/569/571/573 $[M + 1]^+$, 487/489/491 $[M + 1]^+$-HBr, 407/409 $[M + 1]^+$-2HBr, 365/367/369 $[M + 1]^+$-Br-PhCOOH, 327 $[M + 1]^+$-3HBr, 285/287 $[M + 1]^+$-HBr-Br-PhCOOH, 269/271/273 ($C_7H_{11}Br_2$, C9–C15 dibromopyrane, fragment), 121 ($PhCO_2$), 105 (PhCO); HRESIMS *m*/*z*: calcd for $C_{19}H_{21}{}^{79}Br_3NaO_5$ 588.8837 $[M + Na]^+$, found: 588.8826.

4. Conclusions

In conclusion, a new degraded C12 acetogenin–derived substance has been obtained by an unprecedented PCC-catalyzed oxidative cleavage process that adds further insight into our comprehension of the chemistry of this oxidant. Further studies to test the scope of this transformation and its synthetic utility are in progress in our laboratories.

Supplementary Materials: The following are available online, Figure S1: ^{1}H-NMR spectrum of **2**, Figure S2: ^{13}C-NMR spectrum of **2**, Figure S3: ^{1}H-NMR spectrum of **3**, Figure S4: ^{13}C-NMR spectrum of **3**, Figure S5: EIMS spectrum of **3**, Figure S6: HRESIMS spectrum of **3**, Figure S7: FTIR spectrum of **3**.

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Conflicts of Interest: The author declares no conflict of interest.

References

1. Mijs, W.J.; De Jonge, C.R.H.I. (Eds.) *Organic Syntheses by Oxidation with Metal Compounds*; Plenum Press: New York, NY, USA, 1986.
2. Baeckvall, J.-E. (Ed.) *Modern Oxidation Methods*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2010.
3. Piccialli, V. Oxidative cyclization of dienes and polyenes mediated by transition metal oxo-species. *Synthesis* **2007**, 2585–2607. [CrossRef]
4. Piccialli, V. Ruthenium tetroxide and perruthenate chemistry. Recent advances and related transformations mediated by other transition metal oxo-species. *Molecules* **2014**, *19*, 6534–6582. [CrossRef] [PubMed]
5. Piancatelli, G.; Scettri, A.; D'Auria, M. Pyridinium chlorochromate: A versatile oxidant in organic synthesis. *Synthesis* **1982**, 245–258. [CrossRef]
6. Piccialli, V.; Zaccaria, S.; Borbone, N.; Oliviero, G.; D'Errico, S.; Hemminki, A.; Cerullo, V.; Romano, V.; Tuzi, A.; Centore, R. Discovery of a new PCC-mediated stereoselective oxidative spiroketalization process. An access to a new type of poly-THF spiroketal compound displaying anticancer activity. *Org. Biomol. Chem.* **2009**, *7*, 3036–3039. [CrossRef]
7. Piccialli, V.; Zaccaria, S.; Oliviero, G.; D'Errico, S.; D'Atri, V.; Borbone, N. Insight into pyridinium chlorochromate chemistry: Catalytic oxidation of tetrahydrofuran compounds and synthesis of umbelactone. *Eur. J. Org. Chem.* **2012**, *2012*, 4293–4305. [CrossRef]

8. Piccialli, V.; D'Errico, S.; Borbone, N.; Oliviero, G.; Centore, R.; Zaccaria, S. A general synthesis of bis-α-acyloxy-1,4- and -1,5-diketones through catalytic oxidative opening of acylated THF and THP diols. *Eur. J. Org. Chem.* **2013**, *2013*, 1781–1789. [CrossRef]
9. Zaccaria, S.; Borbone, N.; Oliviero, G.; D'Errico, S.; Piccialli, V. Pyridinium chlorochromate chemistry. New insight into oxidation of tetrahydrofurans. *Arkivoc* **2017**, *iv*, 273–290. [CrossRef]
10. Ferraz, H.M.C.; Longo, L.S. Bicyclic β-hydroxytetrahydrofurans as precursors of medium ring keto-lactones. *J. Org. Chem.* **2007**, *72*, 2945–2950. [CrossRef] [PubMed]
11. Song, L.; Liu, Y.; Tong, R. Cephalosporolide B serving as a versatile synthetic precursor: Asymmetric biomimetic total syntheses of cephalosporolides C, E, F, G, and (4-OMe-)G. *Org. Lett.* **2013**, *15*, 5850–5853. [CrossRef] [PubMed]
12. Song, L.; Lee, K.-H.; Lin, Z.; Tong, R. Structural revision of cephalosporolide J and bassianolone. *J. Org. Chem.* **2014**, *79*, 1493–1497. [CrossRef] [PubMed]
13. Wang, J.; Tong, R. Total synthesis of purported cephalosporolides H and I, penisporolide B, and their stereoisomers. *J. Org. Chem.* **2016**, *81*, 4325–4339. [CrossRef] [PubMed]
14. Norris, M.D.; Perkins, M.V. Total synthesis of plakilactones C, B and des-hydroxyplakilactone B by the oxidative cleavage of gracilioether furanylidenes. *J. Org. Chem.* **2016**, *81*, 6848–6854. [CrossRef] [PubMed]
15. Bifulco, G.; Caserta, T.; Gomez-Paloma, L.; Piccialli, V. RuO_4-promoted *syn*-oxidative polycyclization of isoprenoid polyenes: A new stereoselective cascade process. *Tetrahedron Lett.* **2002**, *43*, 9265–9269. [CrossRef]
16. Bifulco, G.; Caserta, T.; Gomez-Paloma, L.; Piccialli, V. Corrigendum to "RuO_4-promoted *syn*-oxidative polycyclization of isoprenoid polyenes: A new stereoselective cascade process": [Tetrahedron Lett. 43 (2002) 9265]. *Tetrahedron Lett.* **2003**, *44*, 3429. [CrossRef]
17. Piccialli, V.; Borbone, N.; Oliviero, G. Ruthenium-catalyzed oxidative cyclization of 1,7-dienes. A novel diasteroselective synthesis of 2,7-disubstituted *trans*-oxepane diols. *Tetrahedron Lett.* **2007**, *48*, 5131–5135. [CrossRef]
18. D'Errico, S.; Oliviero, G.; Borbone, N.; Amato, J.; D'Alonzo, D.; Piccialli, V.; Mayol, L.; Piccialli, G. A facile synthesis of 5′-fluoro-5′-deoxyacadesine (5′-F-AICAR): A novel non-phosphorylable AICAR analogue. *Molecules* **2012**, *17*, 13036–13044. [CrossRef] [PubMed]
19. Giordano, F.; Mayol, L.; Notaro, G.; Piccialli, V.; Sica, D. Structure and absolute configuration of two new polybrominated C15 acetogenins from the sponge *Mycale rotalis*. *Chem. Commun.* **1990**, 1559–1561. [CrossRef]
20. McLafferty, F.W. Mass Spectrometric Analysis... Aliphatic Ethers. *Anal. Chem.* **1957**, *29*, 1782–1789. [CrossRef]
21. Hunsen, M. Pyridinium chlorochromate catalyzed oxidation of alcohols to aldehydes and ketones with periodic acid. *Tetrahedron Lett.* **2005**, *46*, 1651–1653. [CrossRef]
22. Caserta, T.; Piccialli, V.; Gomez-Paloma, L.; Bifulco, G. RuO_4-catalyzed oxidative polycyclization of squalene. Determination of the configuration of the penta-tetrahydrofuranyl diol product. *Tetrahedron* **2005**, *61*, 927–939. [CrossRef]