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Short Note

(±)-((2*S*,5*R*)-5-(Acetoxymethyl)tetrahydrofuran-2-yl)methyl Benzoate

Vincenzo Piccialli

Department of Chemical Sciences, University of Naples Federico II, Via Cintia 4, 80126 Naples, Italy; vinpicci@unina.it

Abstract: In this note we report the synthesis of a doubly acylated *cis*-THF-diol product synthesised in three steps by the stereoselective RuO_4-catalysed oxidative cyclisation of 1,5-hexadiene, followed by benzoylation and acetylation. This substance is one of the substrates chosen to probe a new developed oxidative procedure to transform bis-acylated THF-diols into bis-acylated 1,4-diketones. This new derivative was fully characterised by spectroscopic methods.

Keywords: bis-acylated α-bis-hydroxymethyl-tetrahydrofuran; oxidative cyclization; ^{1}H-NMR; ^{13}C-NMR; FTIR; HRESIMS

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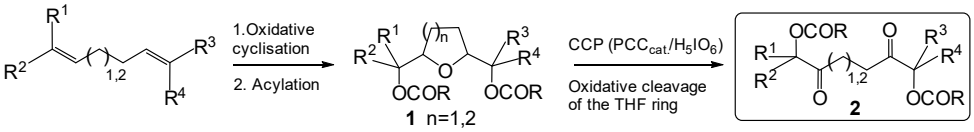
1. Introduction

Oxidation methods, mediated or catalysed by transition metal oxo-species, are a class of processes of central importance in organic synthesis [1–4]. Some of them play an important role in industrial processes [5,6]. As part of our ongoing studies on oxidative processes catalysed by transition metal oxo-species [7–10], we recently developed a new chlorochromatoperiodate (CCP)-catalysed process that allows the synthesis of bis-α-acyloxy-1,4- and -1,5-diketones (**2**, Scheme 1) through the oxidative opening of bis-acylated 2,5-dihydroxyalkyl-substituted tetrahydrofurans and tetrtahydropyrans (acylated THF- and THP-diols, **1**, Scheme 1), respectively [11]. CCP is a powerful reagent, generated by the condensation of pyridinium chlorochromate (PCC) and periodic acid [12], capable of oxidising THF-containing compounds of varying structural complexity [8,9]. Considering that THF- and THP-diols can be synthesised through the ruthenium- [13–17] and osmium- [18,19] catalysed oxidative cyclization of 1,5- and 1,6-dienes (Scheme 1), respectively, our process allows the regioselective bis-ketoacyloxylation of the starting diene.



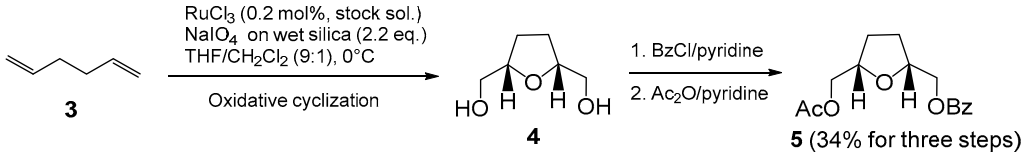
Scheme 1. CCP-catalysed synthesis of bis-α-acyloxy-1,4- and -1,5-diketones.

The keen interest of synthetic organic chemists towards α-acyloxy ketones is demonstrated by the numerous methods developed to obtain these substances (see for example Refs. [20–24]). However, the synthesis and the chemistry of bis-α-acyloxy diketones such as **2** (Scheme 1) are largely unexplored. The possibility of differentiating the chemistry of the two α-acyloxy ketone functionalities, the timing of their synthetic exploitation, as well as the transformation of bis-α-acyloxy diketones into five- or six-membered dihydroxyalkyl-substituted heterocycles, are all appealing synthetic goals. All of the above considerations prompted us to further investigate this transformation, with the aim of also broadening its scope as well as of extending our synthetic procedure to acid or PCC-sensitive substrates. To this end, we planned the synthesis of a set of bis-acylated/bis-protected THF-diols

possessing diverse acyl- or hydroxyl-protecting groups, able to be selectively removed. We report here the synthesis of one of these substances, namely the title compound, that was synthesised by the RuO_4-catalysed stereoselective oxidative cyclisation of commercially available 1,5-hexadiene, followed by the transformation of the alcohol functions into acetate and benzoate groups.

2. Results and Discussion

The oxidative cyclization of 1,5-hexadiene (**3**, Scheme 2) was performed according to a highly efficient RuO_4-catalysed oxidative cyclisation procedure previously developed by Stark and co-workers [15]. The obtained THF-diol product **4** was mono-benzoylated with BzCl in pyridine and then acetylated with Ac_2O/pyridine, to give the title compound **5** which was obtained in pure form by preparative TLC (34% for three steps). Spectral data (^{1}H-and ^{13}C-NMR, FT-IR, HRESIMS) for **5** (see Supplementary Materials) were in full agreement with the reported structure.



Scheme 2. Synthesis of (±)-((2*S*,5*R*)-5-(acetoxymethyl)tetrahydrofuran-2-yl)methyl benzoate (**5**).

3. Materials and Methods

3.1. General Information

All reagents were purchased in the highest commercial quality (Aldrich, Milano, Italy) 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). Na_2SO_4 was used as a drying agent for aqueous work-up. ^{1}H-NMR experiments were performed with a Varian Unity Inova spectrometer (Palo Alto, CA, USA) 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, m = multiplet. Coupling constants are given in Hertz. IR spectrum of **5** was recorded neat with a FT-IR Nicolet 5700 spectrophotometer and is reported in cm^{-1}. The HRMS spectrum of **5** was 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.

3.2. Synthesis of (±)-((2S,5R)-5-(Acetoxymethyl)tetrahydrofuran-2-yl)methyl Benzoate (**5**)

To a suspension of sodium periodate (2.61 g, 26.8 mmol, 2.2 equiv.) absorbed on wet silica (0.64 mmol/g) in tetrahydrofuran/CH_2Cl_2 (9:1, 244 mL), 1,5-hexadiene (1.0 g, 12.2 mmol) was added. The mixture was cooled to 0 °C and ruthenium trichloride (0.2 mol%, 244 µL from a 0.1 M stock solution in H_2O) was added dropwise to the stirred suspension. After the complete conversion of the starting material (1 h, TLC monitoring), the reaction was quenched by the addition of 2-propanol (excess) and the mixture was stirred for a further 5 min and then filtered through a sintered glass funnel. The solid was exhaustively washed with EtOAc and the filtrate taken to dryness to give 1.36 g (85%) of essentially pure **4** (by ^{1}H-NMR) [25], as a clear oil.

Benzoyl chloride (0.5 equiv., 1.64 mmol, 95 µL) was added to crude **4** (217 mg, 1.64 mmol) dissolved in pyridine (1.5 mL) and the mixture was stirred at room temp. for 16 h. At this stage, TLC analysis still revealed the presence of unreacted **4**. To prevent the formation of the bis-benzoylated product, the process was quenched by the addition of water (0.5 mL) and the mixture was stirred for 15 min. and taken to dryness. The product was partitioned between CH_2Cl_2 and water and the organic phase was washed with a sat. aqueous

$NaHCO_3$ solution and then water, dried and then evaporated to give a yellow oil (163.9 mg). NMR analysis showed that this compound was essentially (>90%) the expected mono-benzoylated product.

The crude obtained as above was acetylated with Ac_2O/pyridine overnight and taken to dryness to give a yellow oil. Purification by preparative TLC (silica, hexane/EtOAc, 1:1) afforded the bis-acylated compound **5** (183 mg, 34% for three steps) as a clear oil.

5: IR (neat) ν_{max} 1745 (s), 1720 (s), 1274 (s), 1251 (shoulder), 713 (s) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ8.05 (2H, d, *J* = 8.1), 7.55 (1H, t, *J* = 7.5), 7.43 (2H, t, *J* = 7.6), 4.44–4.37 (1H, m), 4.36–4.29 (1H, m), 4.25–4.17 (1H, m), 4.05–3.98 (1H, m), 2.12–1.99 (5H, m including the acetate methyl singlet), 1.89–1.81 (2H, m), 1.79–1.71 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.9, 166.4, 133.0, 130.0, 129.6, 128.3, 77.5, 77.4, 66.6, 66.5, 27.78, 27.76, 20.8; HRESIMS *m*/*z*: calcd. for $C_{15}H_{18}O_5Na$ 301.1052 $[M + Na]^+$, found: 301.1043.

4. Conclusions

In conclusion, a new bis-acylated *cis*-THF-diol product was synthesised by RuO_4-catalysed oxidative cyclisation of 1,5-hexadiene followed by mono-benzoylation and acetylation. Further studies to test its transformation into the corresponding bis-acylated 1,4-diketone through new oxidative cleavage protocols are in progress in our laboratories. These results will be reported in due course.

Supplementary Materials: The following are available online, Figure S1: ^{1}H-NMR spectrum of **5**, Figure S2: ^{13}C-NMR spectrum of **5**, Figure S3: FTIR spectrum of **5**, Figure S4: HRESIMS of **5**.

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Data Availability Statement: Not applicable.

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

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