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Short Note

(2*S*,2′*S*,4*R*,5*S*,5′*R*)-2,2′-Di-*tert*-butyl-4-hydroxy-5,5′-dimethyl-4,5′-bi(1,3-dioxolanyl)-4′-one

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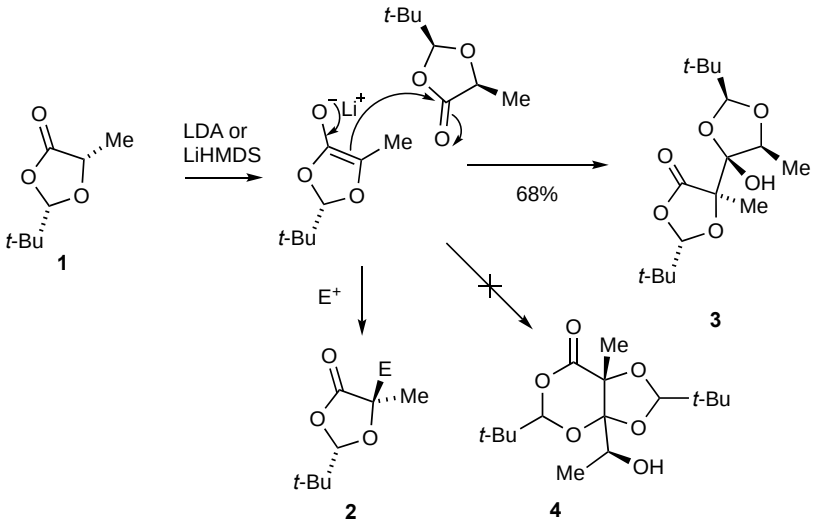
Abstract: The product formed by base-induced dimerisation of (2*S*,5*S*)-2-*tert*-butyl-5-methyl-1,3-dioxolan-4-one is shown by X-ray diffraction to be the title compound and not the isomeric fused-ring 1,3-dioxolane/1,3-dioxane-4-one structure proposed by previous researchers. The analogous compound derived from (2*S*,5*S*)-5-benzyl-2-*tert*-butyl-1,3-dioxolan-4-one has also been obtained and characterised.

Keywords: X-ray structure; structural revision; hydrogen bonding; 1,3-dioxolan-4-one

1. Introduction

Starting with the pioneering work of Seebach almost 40 years ago [1,2], chiral 1,3-dioxolan-4-ones such as **1** derived from (*S*)-lactic acid have proved to be very useful in asymmetric synthesis. As shown in Scheme 1, deprotonation gives an enolate which has lost the stereochemistry at the lactic acid-derived C-5 centre but since overall chirality is preserved by the presence of the bulky *tert*-butyl group at C-2, such enolates react with electrophiles with very high selectivity from the less hindered face to give products **2** with a quaternary centre. Where the reaction also creates a new stereogenic centre within the electrophile, as is the case with aldehydes and ketones [1,2], imines [3], enones [4,5] and nitroalkenes [5,6], this may also be formed with high selectivity and chiral products can be formed even after degradation of the dioxolanone with loss of one or both of the original sterecentres.



Scheme 1. Alkylation and competitive dimerisation of dioxolanone **1** upon treatment with a base.

Even in the earliest papers, it was noted that formation of more concentrated enolate solutions from **1** led, as a side reaction, to interaction of the enolate with a molecule of the

Citation: Aitken, R.A.; Power, L.A.; Slawin, A.M.Z. (2*S*,2′*S*,4*R*,5*S*,5′*R*)-2,2′-Di-*tert*-butyl-4-hydroxy-5,5′-dimethyl-4,5′-bi(1,3-dioxolanyl)-4′-one. *Molbank* **2023**, *2023*, M1699. https://doi.org/10.3390/M1699

Received: 9 June 2023
Revised: 14 July 2023
Accepted: 17 July 2023
Published: 20 July 2023

precursor **1** to form a dimer which was assigned the structure **4** [1,2] and this byproduct was also reported by later researchers [3]. In our own research [4,5], we have also obtained this dimeric product and were curious as to the mechanism of its formation. In this paper, we re-examine the structure of this product and show that the originally assigned structure is not correct.

2. Results and Discussion

When a solution of dioxolanone **1** was added to a solution of LDA or LiHMDS at −78 °C in the presence of a range of electrophiles, the dimer was obtained as a byproduct. Particularly when the dioxolanone was added too rapidly to the base, this became the major product and was obtained in up to 68% isolated yield. The compound exhibited physical and spectroscopic properties in excellent agreement with those reported for **4** with the ^{1}H and ^{13}C NMR data (see Supplementary Materials) clearly showing the presence of two distinct OCH(*t*-Bu)O units, a lactone C=O, two distinct methyl groups, one joined to a quaternary centre and the other forming a C–CH(Me)–O unit, two quaternary sp^{3} carbons, one joined to a single oxygen and the other to two oxygens, and a free hydroxyl group. On the face of it, these data are in full agreement with the reported structure **4**. However, we could not come up with a reasonable mechanism for the formation of this structure and noted that the more obvious dimer **3**, simply formed by a nucleophilic attack of the enolate at the lactone carbonyl of **1** followed by protonation on workup, also fits the spectroscopic data.

Crystals suitable for X-ray diffraction were obtained and the resulting molecular structure (Figure 1) confirmed that the compound was indeed **3**. No attempt was made to determine the absolute configuration crystallographically since the configuration of the two newly formed centres linking the five-membered rings could be observed relative to the two invariant CH*t*-Bu centres. As expected, it is the stereoisomer derived from attack of the least hindered face of the enolate at the least hindered face of the carbonyl group in **1** (Scheme 1).

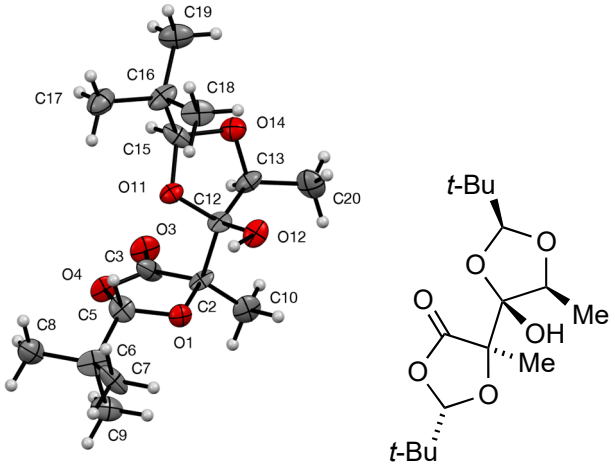


Figure 1. The molecular structure of **3** (50% probability ellipsoids) showing the numbering system used and conventional representation.

The crystal structure was found to consist of hydrogen-bonded chains along the *a*-axis with O–H . . . O=C bonding (Figure 2, Table 1): in terms of the Etter–Bernstein [7] graph set description, a *C*(6) interaction.

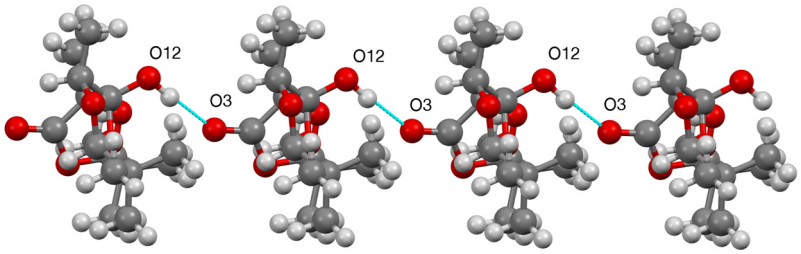
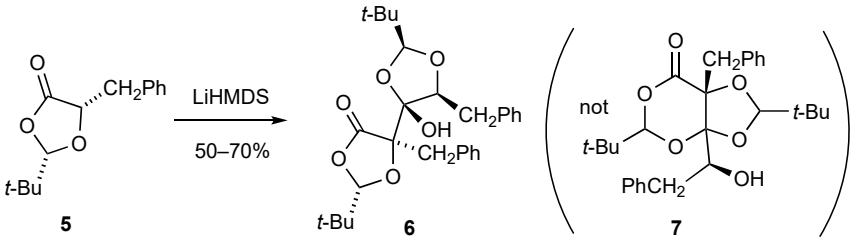


Figure 2. Hydrogen-bonding pattern for compound **3**.

Table 1. Hydrogen-bonding parameters for **3** (Å, °).

D—H . . . A	D—H	H . . . A	D . . . A	D—H . . . A
O(12)–H(12) . . . O(3)	0.98	1.88	2.853(10)	174.5

As also noted earlier [2], this is a general reaction of these dioxolanones and we also obtained the dimeric product from reactions of **5** in higher purity than before as judged from the increased value of the optical rotation. This again showed ^{1}H NMR spectroscopic data in good agreement with the reported values [2], but we were able to analyse this in more detail and also record the ^{13}C NMR spectrum for the first time (see Supplementary Materials). Based on the similarity with **3**, we suggest that this also has the structure **6** rather than the isomeric structure **7** previously reported (Scheme 2) [2].



Scheme 2. Dimerisation of dioxolanone **5** upon treatment with the base giving **6.**

3. Experimental

Melting points were recorded on a Reichert hot-stage microscope (Reichert, Vienna, Austria) and are uncorrected. Optical rotation measurements were made using an Optical Activity 1000 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. Elemental analysis was conducted using a Carlo Erba CHNS analyser. Mass spectra were obtained using a Micromass instrument using electrospray ionisation. IR spectra were recorded on a Perkin-Elmer 1420 instrument (Perkin-Elmer, Waltham, MA, USA). NMR spectra were obtained for ^{1}H at 300 MHz and for ^{13}C at 75 MHz using a Bruker AV300 instrument (Bruker, Billerica, MA, USA). Spectra were run at 25 °C on solutions in $CDCl_3$ with internal Me_4Si as the reference. Chemical shifts are reported in ppm to high frequency of the reference and coupling constants *J* are in Hz. The dioxolanones **1** and **5** were prepared using the literature method described in [2].

3.1. Formation of (2S,2′S,4R,5S,5′R)-2,2′-Di-tert-butyl-4-hydroxy-5,5′-dimethyl-4,5′-bi(1,3-dioxolanyl)-4′-one **3**

To a solution of lithium hexamethyldisilazide (13.2 mmol) in THF (50 mL) stirred at −78 °C under nitrogen was added dropwise a solution of (2*S*,5*S*)-2-*t*-butyl-5-methyl-1,3-dioxolan-4-one **1** (2.00 g, 12.7 mmol) in dry THF (10 mL), followed after 45 min by a solution of 4-methoxy-β-nitrostyrene (2.56 g, 13.2 mmol) in THF (5 mL). The mixture was stirred at −20 °C for 2 h. Addition to sat. aq. ammonium chloride (50 mL) was followed by extraction with diethyl ether (3 × 20 mL), drying and evaporation. Chromatography of the residue (SiO_2, hexane/Et_2O, 2:1) gave the product **3** as colourless crystals (1.36 g, 68%), mp 156 °C

(Lit. [1] 147 °C); $[\alpha]_D$ +22.66 (c = 0.75, CH_2Cl_2) (Lit. [1] +21.5); Elemental analysis: found C 61.2, H 8.7. $C_{16}H_{28}O_6$ requires C 60.7, H 8.9%; HRMS (ES): found 339.1780. $C_{16}H_{28}O_6Na$ (M + Na) requires 339.1784; ν_{max}/cm^{-1} 3479, 1776, 1374, 1351, 1285, 1264 and 1182; δ_H 0.91 (9 H, s, *t*-Bu), 0.98 (9 H, s, *t*-Bu), 1.35 (3 H, d, *J* 6.2, Me), 1.41 (3 H, s, Me), 3.12 (1 H, br s, OH), 4.36 (1 H, dq, *J* 6.2, 0.78, CH-Me), 4.53 (1 H, s, CH-*t*-Bu) and 5.35 (1 H, s, CH-*t*-Bu); δ_C 13.9 (Me), 18.8 (Me), 23.3 (*t*-Bu), 24.0 (*t*-Bu), 33.5 (C-*t*-Bu), 34.5 (C-*t*-Bu), 75.7 (C-5), 83.0 (C-5′), 102.0 (C-OH), 109.7 (CH), 110.0 (CH) and 172.4 (C=O).

3.2. X-ray Structure Determination of ***3***

Crystal data for $C_{16}H_{28}O_6$, M = 316.38, colourless platelet, crystal dimensions 0.10 × 0.10 × 0.03 mm, monoclinic, space group C2 (No. 5), a = 20.893(9), b = 6.144(3), c = 13.864(7) Å, β = 102.06(3)°, V = 1740.5(14) Å^3, Z = 4, D_{calc} = 1.207 g cm^{-3}, T = 93(2) K, $R1$ = 0.1370, $Rw2$ = 0.3278 for 2021 reflections with I > 2 σ (I) and 200 variables. Data were collected on a Bruker SMART diffractometer with graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) and have been deposited at the Cambridge Crystallographic Data Centre as CCDC 2240551 The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/getstructures. The structure was solved by direct methods and refined by full-matrix least-squares against F2 (SHELXL, Version 2018/3 [8]).

3.3. Formation of (2S,2′S,4′R,5S,5′R)-5,5′-Dibenzyl-2,2′-di-tert-butyl-4-hydroxy-4,5′-bi [1,3-dioxolanyl]-4′-one ***6***

To a solution of lithium hexamethyldisilazide (2.1 mmol) in dry THF (10 mL) stirred at −78 °C under nitrogen was added dropwise a solution of dioxolanone **5** (0.50 g, 2.0 mmol) in THF (3 mL), followed after 15 min by a solution of ethyl crotonate (0.23 g, 2.1 mmol) in THF (3 mL). The mixture was stirred at −78 °C for 30 min then allowed to warm slowly up to RT. Addition to sat. aq. ammonium chloride (20 mL) was followed by extraction with diethyl ether (3 × 10 mL), drying and evaporation. Chromatography of the residue (SiO_2, hexane/Et_2O, 7:3) gave the product **6** (0.35 g, 70%) as colourless crystals, mp 174–175 °C (Lit. [2] 209–211 °C subl.); $[\alpha]_D$ −45 (c = 1, CH_2Cl_2) (Lit. [2] −38.9); Elemental analysis: found C, 71.6; H, 7.7. $C_{28}H_{36}O_6$ requires C, 71.8; H, 7.7%; ν_{max}/cm^{-1} 3447, 2960, 1770, 1150; δ_H 0.51 (9 H, s, *t*-Bu), 0.93 (9 H, s, *t*-Bu), 2.96 (1 H, dd, *J* 14, 4, CH_2), 3.07 (1 H, d, *J* 14, CH_2), 3.13 (1 H, dd, *J* 14, 10, CH_2), 3.23 (1 H, d, *J* 14, CH_2), 3.37 (1 H, br s, OH), 4.56 (1H, dd, *J* 10, 4, CH-Bn), 4.58 (1 H, s, CH-*t*-Bu), 5.33 (1 H, s, CH-*t*-Bu) and 7.18–7.36 (10 H, m, Ph); δ_C 23.0 (*t*-Bu), 24.1 (*t*-Bu), 33.7 (C-Me_3), 33.9 (C-Me_3), 36.0 (CH_2), 37.3 (CH_2), 80.7 (CH-Bn), 87.0 (C-Bn), 102.7 (C-OH), 110.0 (CH-*t*-Bu), 110.5 (CH-*t*-Bu), 126.5 (CH), 127.3 (CH), 128.4 (2CH), 128.5 (2CH), 129.3 (2CH), 130.9 (2CH), 133.7 (Ph-C1), 138.4 (Ph-C1) and 171.5 (C=O); m/z (ES) 491.14 (M + Na^+, 100%).

Supplementary Materials: The following is available online: ^1H and ^{13}C NMR data for **3** and **6**, cif and check-cif files for **3**.

Author Contributions: L.A.P. prepared the compounds; A.M.Z.S. collected the X-ray data and solved the structure; R.A.A. designed the study, analysed the data and wrote the paper. All authors have read and agreed to the published version of the manuscript.

Funding: We thank the School of Chemistry for a studentship to L.A.P.

Data Availability Statement: As noted above the X-ray diffraction data have been deposited at CCDC.

Conflicts of Interest: The authors declare no conflict of interest.

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