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Full Paper

The Conversion of Levoglucosenone into Isolevoglucosenone*

Xinghua Ma,[A] *Natasha Anderson,*[A] *Lorenzo V. White,*[A] *Song Bae,*[A] *Warwick Raverty,*[B] *Anthony C. Willis,*[A] *and Martin G. Banwell*[A,C]

[A]Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra ACT 2601, Australia.
[B]Circa Group Pty Ltd, 34 Norfolk Court, Coburg North Vic. 3058, Australia.
[C]Corresponding author. Email: Martin.Banwell@anu.edu.au

Levoglucosenone (**1**), a compound that will soon be available in tonne quantities through the pyrolysis of acid-treated lignocellulosic biomass, has been converted into isolevoglucosenone (**2**) using Wharton rearrangement chemistry. Treatment of compound **1** with alkaline hydrogen peroxide gave the γ-lactones **5** and **6** rather than the required epoxy-ketones **3** and/or **4**. However, the latter pair of compounds could be obtained by an initial Luche reduction of compound **1**, electrophilic epoxidation of the resulting allylic alcohol **8** and oxidation of the product oxiranes **9** and **10**. Independent treatment of compounds **3** and **4** with hydrazine then acetic acid followed by oxidation of the ensuing allylic alcohols finally afforded isolevoglucosenone (**2**). Details of the single-crystal X-ray analyses of epoxy-alcohols **9** and **10** are reported.

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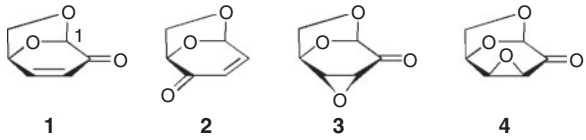
Introduction

The pyrolysis of mineral acid-impregnated waste paper provides a means for generating the 1,6-anhydro-bridged monosaccharide derivative levoglucosenone (**1**).[1] Indeed, recent refinements of this now rather well-known process mean that compound **1** will soon be produced in tonne quantities under pilot plant conditions.[2] Given its origins, chirality, and associated functionalities, levoglucosenone is receiving increasing attention as a sustainably produced and potentially versatile chiral pool material. Indeed, over the preceding 30 years or so, it has received significant attention as a starting material in the chemical synthesis of a range of target compounds including various biologically active natural products, sugar mimetics, and agrochemicals. Much of the work in the area has been reviewed recently.[3] The quasi-enantiomerically related[4] compound isolevoglucosenone (**2**),[3a,5] which can be obtained from D-glucose in four chemical steps,[5b] has received less attention as a starting point in chemical synthesis, perhaps in part because its preparation by the means just mentioned has been described as 'labour intensive'.[6] Accordingly, the development of simple methods for effecting the conversion **1** → **2** is likely to be useful. The first attempts to do so were reported in 1986 by Furneaux and coworkers[7] who demonstrated that the product arising from the conjugate addition of benzyl alcohol to compound **1** could be elaborated over a further five steps into isomer **2**. More recently, Witczak et al.[6] detailed a four-step sequence involving, as the pivotal transformation, a 2,3-sigmatropic rearrangement of an allylic selenide as a means for effecting the conversion **1** → **2**.



1 **2** **3** **4**

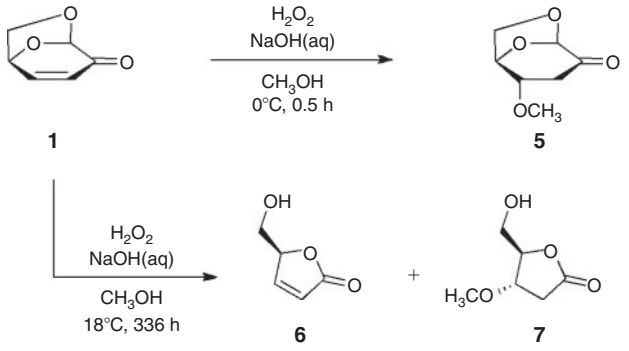
Chart 1.

The Wharton rearrangement reaction often provides a concise, inexpensive, and operationally simple means for effecting, via the corresponding epoxy-ketones, the 1,3-transposition of α,β-unsaturated enones.[8] However, this protocol does not appear to have been explored as a means for converting levoglucosenone into congener **2**. Accordingly, we sought to examine such possibilities and now detail syntheses of the relevant and stereoisomeric epoxy-ketones **3** and **4** (from compound **1**) and report on their participation in the Wharton rearrangement reaction (Chart 1).[3]

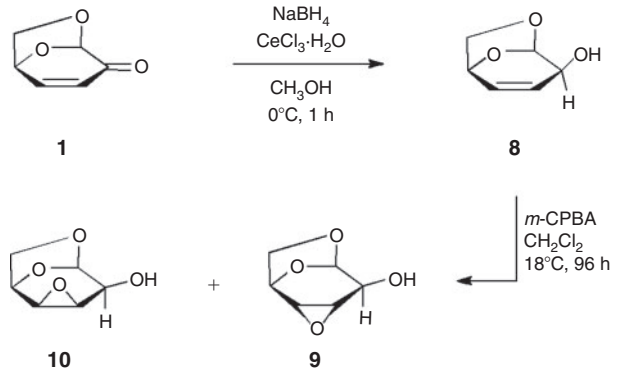
Results and Discussion

In initial attempts to form epoxy-ketone **3** and/or its isomer **4**, a methanolic solution of levoglucosenone (**1**) was treated at 0°C with a mixture of aqueous hydrogen peroxide and sodium hydroxide (Scheme 1). Thin-layer chromatographic analysis of the reaction mixture after just 0.5 h revealed essentially complete consumption of the starting material and the more-or-less exclusive formation of a chromatographically less mobile and

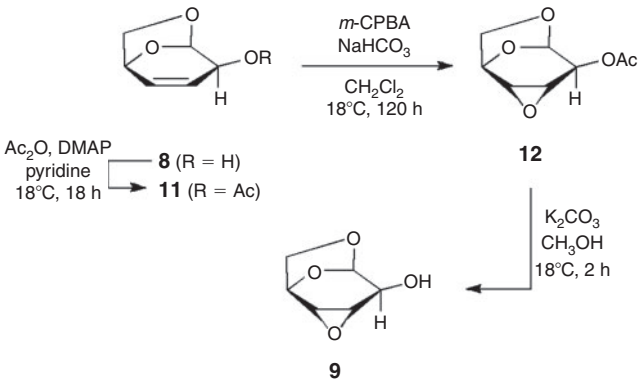
*Dedicated to the memory of Sir John 'Kappa' Cornforth, a legendary scientist and an inspirational human being.



Scheme 1.



Scheme 2.



Scheme 3.

non-chromophoric product. After aqueous workup and chromatographic purification, a crystalline product was obtained, and single-crystal X-ray analysis revealed it to be the ether **5**[9] (64 %). This presumably arises from conjugate addition of the elements of methanol to substrate **1** and with the stereochemical course of the reaction being dictated by the steric demands of the 1,6-anhydro-bridge that ensure preferential delivery of any nucleophiles to the α-face of the enone system.

In another attempt to effect the conversion **1** → **3** and/or **4**, the first of these compounds was treated with the same reagents as defined above but now at ambient temperatures and for a period of 336 h. Such conditions were investigated on the basis that the formation of ether **5** from levoglucosenone might be a reversible process and that there could, therefore, be a low steady-state concentration of the latter compound present in the reaction mixture that was available to engage in the desired nucleophilic epoxidation process. In the event, however, the only products isolated from the reaction mixture proved to be the previously reported hydroxymethylated butenolide **6**[10] (13 %) and the related methanol addition product **7**[11] (4 %). The former product is presumably derived from a Baeyer–Villiger type oxidation of substrate **1** to give an internal *ortho*-ester that is itself hydrolyzed under the alkaline conditions. After γ-lactonization and loss of C1 (levoglucosenone numbering) as a formate ion compound **6** would then be formed. Interestingly, the present work appears to represent the first time compound **6** has been reported to be formed directly from levoglucosenone rather than by a two-step process as described by Koseki et al.[10] That having been said, the latter process is much more efficient.

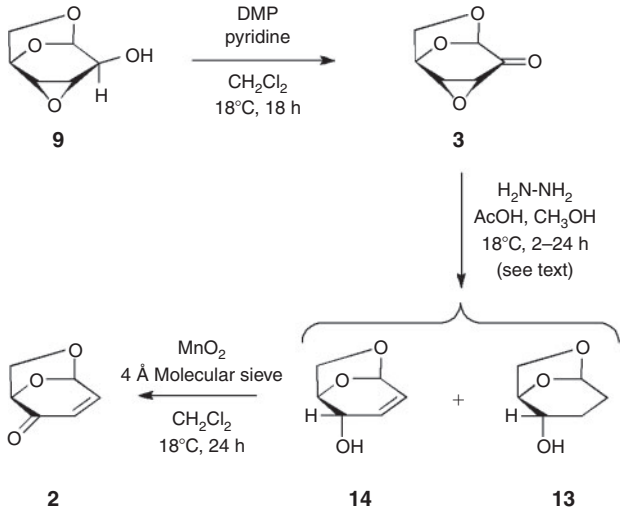
In light of our inability to prepare epoxy-ketones **3** and/or **4** by direct nucleophilic epoxidation of levoglucosenone, we elected to apply electrophilic protocols for this same purpose. To such ends, and as shown in Scheme 2, enone **1** was reduced under Luche conditions to give, in an almost completely stereoselective manner, the previously reported allylic alcohol **8**[1,12] that was obtained in 91 % yield as a white, crystalline solid.

Epoxidation of the latter compound using *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane afforded a chromatographically separable mixture of the diastereoisomeric epoxy alcohols **9**[13] (56 %) and **10**[12,13] (31 %), the structures of which were both established by single-crystal X-ray analyses.[14] Clearly, the 'blocking' effect of the 1,6-anhydro-bridge within substrate **8** results in the preferential formation of the α-epoxide **9** although this does not completely overwhelm the directing capacities of the hydroxyl group with the result that reasonably significant quantities of the β-epoxide **10** are still formed.

A completely diastereoselective electrophilic epoxidation reaction was observed (Scheme 3) when the readily derived acetate **11**[15] (90 %) of allylic alcohol **8** was subjected to reaction with *m*-CPBA in dichloromethane. Specifically, in the absence of any possible hydroxyl-based directing effects, the epoxy-acetate **12**[15] (73 %) is obtained as the only isolable product of reaction and its structure follows from its conversion into epoxy-alcohol **9** (96 %) on exposure to potassium carbonate in methanol.

In agreement with earlier observations,[13] compounds **9** and **10** proved to be rather stable species that showed little or no propensity, at least upon manipulation in organic solvents under non-basic conditions, to engage in Payne rearrangement reactions and thereby affording the isomeric and so-called Černý epoxides.[16] Gratifyingly, when the former compound was subjected to reaction (Scheme 4) with the Dess–Martin periodinane (DMP) in dichloromethane containing 10 molar equivalents (with respect to **9**) of pyridine, the anticipated epoxy-ketone **3**[17] was obtained as a white, crystalline solid in 98 % yield. Treatment of the latter with hydrazine and, after 1 h, with acetic acid (AcOH) and then allowing the resulting mixture to stand at room temperature for 24 h afforded a chromatographically separable mixture of the saturated alcohol **13**[18] (23 %) and the anticipated allylic alcohol **14**[9] (21 %), the structure of which was confirmed by single-crystal X-ray analysis. The yield of the latter product could be increased to 45 % by reducing the standing time of the reaction to 2 h.

Product **13** is thought to arise because the precursor epoxy-ketone **3** contained, despite extensive efforts to remove them,



Scheme 4.

traces of DMP that oxidizes the hydrazine to di-imide, which reduces the C=C bond of the primary product **14** to its saturated counterpart (i.e. **13**). Presumably, the reduced form of the DMP generated in this process is 'recycled' by atmospheric oxygen.[19] In keeping with such proposals, when a sample of pure allylic alcohol **14** was treated in a vessel open to the air with a combination of hydrazine, acetic acid, and 2 mol-% DMP at ambient temperatures for 48 h, compound **13** was obtained in a yield of 77 % (at 62 % conversion) after column chromatography.

The completion of the synthesis of isolevoglucosenone from epoxy-ketone **3** (Scheme 4) simply involved treating the allylic alcohol **14** with a suspension of manganese dioxide[20] and 4 Å molecular sieves in dichloromethane at 18°C for 24 h. After flash column chromatography, the target enone **2**[5–7,21] was obtained in 65 % yield as a clear, colourless oil. The derived spectral data were in good agreement with those reported previously. In particular, the NMR data (Table 1) derived from the material prepared by the route described here proved an excellent match with those reported[21] by Ogasawara and coworkers for samples of (+)-isolevoglucoseone (**2**) obtained from 2-vinylfuran using Sharpless asymmetric dihydroxylation protocols.

The conversion of the epoxy-alcohol **10** into enone **2** followed the same pathway (Scheme 5) as used above. Specifically, the former compound was oxidized to the corresponding and previously reported epoxy-ketone **4**[17] using DMP and the latter was then subjected to a Wharton rearrangement reaction by successive treatment with hydrazine then acetic acid. In keeping with earlier observations, the use of an extended (24 h) reaction time led to a chromatographically separable mixture of the saturated alcohol **15**[18] (61 %) and its (targeted) unsaturated counterpart **16**[5] (7 %). However the latter product could be obtained as the essentially exclusive product of reaction (57 %) if a shorter reaction period (1 h) was used. Oxidation of compound **16** with manganese dioxide in the presence of 4 Å molecular sieves then gave isolevoglucosenone (**2**), this time in 62 % yield.

Conclusions

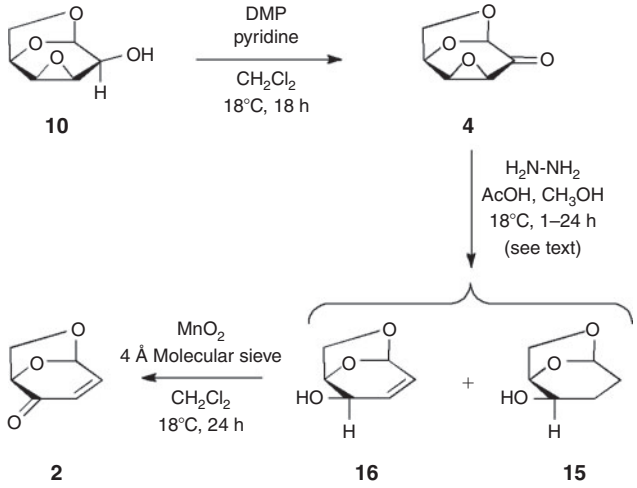
A relatively straightforward five-step method for converting potentially abundant levoglucosenone (**1**) into isomer **2** has been developed. The pivotal transformation is the Wharton rearrangement of epoxy-ketones **3** and **4** that cannot be formed directly from compound **1** using nucleophilic epoxidation procedures because of the intervention of competing Baeyer–Villiger oxidation reactions. As such, electrophilic epoxidation of the allylic alcohol **8** derived by 1,2-reduction of compound **1** and oxidation of the resulting epoxy-alcohols was used as the means for obtaining the necessary epoxy-ketones **3** and **4**.

Though all of the compounds described herein have been the subjects of previous reports, the described reaction sequences provide a new route to isolevoglucosenone (**2**) that employs simple and conventional reagents and with these being deployed under operationally straightforward conditions. As such, and given the ease of access to precursor **1**, compound **2** should now be more readily available as a chiron for assembling a range of biologically relevant molecules.

Table 1. Comparison of the ^{13}C and ^{1}H NMR data recorded for isolevoglucosenone (2) obtained by the pathway reported here with those reported by Ogasawara

^{13}C NMR data for compound **2** (δ_C)		^{1}H NMR data for compound **2** (δ_H)	
Present work[A]	Ogasawara[B]	Present work[C]	Ogasawara[D]
194.5	194.7	7.13 (dd, *J* 9.8, 3.4, 1H)	7.14 (dd, *J* 9.9, 3.3, 1H)
147.3	147.5	6.11 (d, *J* 9.8, 1H)	6.11 (dt, *J* 9.9, 1.1, 1H)
127.1	127.1	5.81 (d, *J* 3.4, 1H)	5.82 (dd, *J* 3.3, 0.5, 1H)
96.1	96.0	4.78 (d, *J* 6.3, 1H)	4.79 (dt, *J* 6.3, 1.4, 1H)
79.6	79.6	4.11 (m, 1H)	4.12 (dd, *J* 8.2, 6.3, 1H)
62.7	62.6	3.66 (dm, *J* 6.3, 1H)	3.66 (dd, *J* 8.2, 1.4, 1H)

[A]Data recorded in $CDCl_3$ at 125 MHz.
[B]Data obtained from ref. [21a] and recorded in $CDCl_3$ at 150 MHz.
[C]Data recorded in $CDCl_3$ at 500 MHz.
[D]Data obtained from ref. [21a] and recorded in $CDCl_3$ at 300 MHz.



Scheme 5.

Experimental

General Experimental Procedures

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18°C in base-filtered $CDCl_3$ on a Varian spectrometer operating at 400 or 500 MHz for proton and

100 or 125 MHz for carbon nuclei. For ^{1}H NMR spectra, signals arising from the residual protio forms of the solvent were used as the internal standards. ^{1}H NMR data are recorded as follows: chemical shift (δ) (multiplicity, coupling constant(s) *J* (Hz), relative integral), where multiplicity is defined as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ 'triplet' appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR spectrometer. Samples were analyzed as thin films on KBr plates. Low-resolution electrospray ionization (ESI) mass spectra were recorded on a Micromass LC-ZMD single quadrupole liquid chromatograph–mass spectrometer, whereas high-resolution measurements were conducted on an LCT Premier time-of-flight instrument. Low- and high-resolution electron impact (EI) mass spectra were recorded on an Autospec Premier Micromass magnetic-sector machine. Optical rotations were recorded in $CHCl_3$ at 20°C on a Perkin–Elmer 343 Polarimeter. Melting points were measured on an Optimelt automated melting point system and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on aluminium-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (concentrated) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5 % sodium hydroxide aqueous solution : water (3 g : 20 g : 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[22] with silica gel 60 (40–63 μm) as the stationary phase and using the analytical reagent (AR)- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from Sigma–Aldrich, Merck, TCI, Strem, or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from AJAX, BDH, or Unilab Chemical Companies. Tetrahydrofuran (THF), methanol, and dichloromethane were dried using a Glass Contour™ solvent purification system that is based on a technology originally described by Grubbs et al.[23] Where necessary, reactions were performed under an inert atmosphere.

Specific Synthetic Transformations

Compound **5**: A magnetically stirred solution of levoglucosenone (**1**) (100 mg, 0.79 mmol) in methanol (5 mL) was cooled to 0°C then treated with hydrogen peroxide (240 μL of a 9.79 M aqueous solution, 2.37 mmol) and sodium hydroxide (5 drops of a 5 M aqueous solution). After 0.5 h, the reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow residue thus obtained was subjected to flash chromatography (silica, 1 : 2 v/v acetone/hexane elution) and concentration of the relevant fractions (R_F 0.4) gave compound **5**[9] (81 mg, 64 %) as a white, crystalline solid, mp 94.5–95.9°C. ν_{max} (KBr)/cm^{-1} 2974, 2908, 2831, 1742, 1210, 1118, 1088, 969, 909, 897, 484. δ_H ($CDCl_3$, 400 MHz) 5.14 (s, 1H), 4.80 (m, 1H), 3.97 (dd, *J* 7.9, 5.6, 1H), 3.89 (d, *J* 7.9, 1H), 3.74 (d, *J* 5.8, 1H), 3.41 (s, 3H), 2.72 (dd, *J* 17.1, 5.8, 1H), 2.57 (d, *J* 17.1, 1H). δ_C ($CDCl_3$, 100 MHz) 198.1, 101.3, 78.6, 74.4, 65.1, 56.6, 36.9. *m/z* (ESI, +ve) 197 (13 %, $[M + K]^+$), 181 (100 %, $[M + Na]^+$), 159 (79 %, $[M + H]^+$). *m/z* (HRMS ESI (+ve)) 181.0447; $[M + Na]^+$ requires 181.0447.

Compounds **6** and **7**: A magnetically stirred solution of compound **1** (200 mg, 1.59 mmol) in methanol (5 mL) maintained at 18°C was treated with H_2O_2 (250 μL of a 30 % aqueous solution, 7.93 mmol) then NaOH (175 μL of a 0.5 M aqueous solution). After 72 h, additional amounts of H_2O_2 (100 μL of a 30 % aqueous solution, 3.18 mmol) and NaOH (70 μL of a 0.5 M aqueous solution) were introduced, and stirring continued for a further 336 h before the reaction mixture was concentrated under reduced pressure. The light yellow residue obtained was subjected to flash chromatography (silica, 5 : 4 v/v ethyl acetate/hexane → 5 : 4 : 0.5 v/v/v ethyl acetate/hexane/methanol gradient elution) afforded two fractions A and B.

Concentration of fraction A (R_F 0.5 in 7 : 2 : 1 v/v/v ethyl acetate/hexane/methanol) provided compound **7**[11] (10 mg, 4 %) as a light yellow oil. ν_{max} (KBr)/cm^{-1} 3426, 2937, 2834, 1770, 1634, 1368, 1181, 1094, 935. δ_H ($CDCl_3$, 400 MHz) 4.50 (m, 1H), 4.12 (m, 1H), 3.95 (dd, *J* 12.7, 2.9, 1H), 3.75 (dm, *J* 12.7, 1H), 3.35 (s, 3H), 2.88 (dm, *J* 17.1, 1H), 2.55 (dd, *J* 17.1, 2.9, 1H), 2.40 (broad s, 1H). δ_C ($CDCl_3$, 125 MHz) 175.9 (C), 85.3 (CH), 77.6 (CH), 62.5 (CH_2), 56.7 (CH_3), 35.4 (CH_2). *m/z* (ESI, +ve) 169 (100 %, $[M + Na]^+$). *m/z* (HRMS ESI (+ve)) 169.0477; $[M + Na]^+$ requires 169.0477.

Concentration of fraction B (R_F 0.4 in 7 : 2 : 1 v/v/v ethyl acetate/hexane/methanol) provided compound **6**[10] (24 mg, 13 %) as a light yellow oil. ν_{max} (KBr)/cm^{-1} 3400, 2932, 1745, 1602, 1331, 1170, 1112, 1080, 1053, 862, 820. δ_H ($CDCl_3$, 500 MHz) 7.49 (m, 1H), 6.19 (m, 1H), 5.16 (m, 1H), 4.00 (dm, *J* 12.2, 1H), 3.78 (dd, *J* 12.2, 4.8, 1H), 2.64 (s, 1H). δ_C ($CDCl_3$, 75 MHz) 173.2 (C), 153.6 (CH), 122.9 (CH), 84.1 (CH), 62.3 (CH_2). *m/z* (EI, 70 eV) 84 (100 %, $[M - HOCH_2\bullet]^+$). *m/z* (HRMS ESI (+ve)) 137.0215; $[M + Na]^+$ requires 137.0215.

Compound **8**: A solution of compound **1** (1.00 g, 7.93 mmol) in methanol (25 mL) maintained at 0°C was treated with $CeCl_3{\cdot}7H_2O$ (3.00 g, 8.05 mmol) then (cautiously) with $NaBH_4$ (300 mg, 7.93 mmol). After stirring for 1 h, the reaction mixture was concentrated under reduced pressure and the residue thus obtained was subjected to flash chromatography (silica, 2 : 1 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_F 0.5 in 5 : 4 : 1 v/v/v ethyl acetate/hexane/methanol) afforded compound **8**[12] (922 mg, 91 %) as a white, crystalline solid, mp 64–66°C (lit. 65.6–66.4°C[12]). ν_{max} (KBr)/cm^{-1} 3402, 2956, 2891, 1638, 1402, 1347, 1122, 1066, 1045, 979, 821. δ_H ($CDCl_3$, 500 MHz) 6.10 (dddd, *J* 9.8, 5.4, 4.4, 1.0, 1H), 5.70 (m, 1H), 5.50 (m, 1H), 4.65 (t, *J* 4.4, 1H), 4.32 (m, 1H), 3.83 (d, *J* 6.4, 1H), 3.74 (m, 1H), 2.13 (s, 1H). δ_C ($CDCl_3$, 125 MHz) 130.7 (CH), 129.1 (CH), 101.2 (CH), 71.1 (CH), 70.6 (CH_2), 68.7 (CH). *m/z* (ESI, +ve) 151 (100 %, $[M + Na]^+$). *m/z* (HRMS ESI (+ve)) 151.0371; $[M + Na]^+$ requires 151.0371.

Compounds **9** and **10**: *m*-CPBA (5.20 g of material of 77 % purity, 23.20 mmol) was added to a magnetically stirred solution of compound **8** (740 mg, 5.78 mmol) in dichloromethane (80 mL) maintained at 18°C. After 96 h, the reaction mixture was concentrated under reduced pressure and the residue so obtained subjected to flash chromatography (silica, 1 : 1 v/v ethyl acetate/hexane → 5 : 4 : 0.3 v/v/v ethyl acetate/hexane/methanol gradient elution) to deliver two fractions, A and B.

Concentration of fraction A (R_F 0.5 in 6 : 3 : 1 v/v/v ethyl acetate/hexane/methanol) gave compound **10**[12,13] (259 mg, 31 %) as a white, crystalline solid, mp 71–73°C (lit. 74.0–75.2°C[12]). $[\alpha]_D$ −56° (*c* 0.5 in methanol). ν_{max} (KBr)/cm^{-1} 3365, 2960, 2900, 1423, 1245, 1147, 1063, 973, 916, 816. δ_H

($CDCl_3$, 500 MHz) 5.29 (d, *J* 3.4, 1H), 4.81 (t, *J* 4.9, 1H), 3.99 (d, *J* 6.9, 1H), 3.78 (m, 2H), 3.55 (m, 1H), 3.33 (m, 1H), 2.34 (d, *J* 9.0, 1H). δ_C ($CDCl_3$, 125 MHz) 97.8 (CH), 71.7 (CH), 66.5 (CH), 63.9 (CH_2), 57.3 (CH), 50.2 (CH). *m/z* (ESI, +ve) 167 (100 %, $[M + Na]^+$. *m/z* (HRMS ESI (+ve)) 167.0320; $[M + Na]^+$ requires 167.0320.

Concentration of fraction B (R_F 0.4 in 6 : 3 : 1 v/v/v ethyl acetate/hexane/methanol) gave compound **9**[13] (466 mg, 56 %) as a white, crystalline solid, mp 158–160°C. $[\alpha]_D$ −129° (*c* 0.5 in methanol). ν_{max} (KBr)/cm^{-1} 3386, 2973, 2907, 1489, 1414, 1084, 1053, 974, 948, 874, 808, 468. δ_H ($CDCl_3$, 500 MHz) 5.32 (m, 1H), 4.73 (d, *J* 3.9, 1H), 4.05 (d, *J* 7.3, 1H), 3.87–3.83 (complex m, 2H), 3.13 (d, *J* 3.9, 1H), 3.00 (m, 1H), 2.36 (d, *J* 9.0, 1H). δ_C ($CDCl_3$, 125 MHz) 99.1 (CH), 69.8 (CH), 67.3 (CH_2), 65.0 (CH), 51.0 (CH), 50.0 (CH). *m/z* (ESI, +ve) 167 (100 %, $[M + Na]^+$. *m/z* (HRMS ESI (+ve)) 167.0320; $[M + Na]^+$ requires 167.0320.

Compound **11**: A magnetically stirred solution of compound **8** (166 mg, 1.30 mmol) in pyridine (5 mL) maintained at 18°C was treated with acetic anhydride (Ac_2O; 500 µL, 5.29 mmol) and 4-dimethylaminopyridine (DMAP; 20 mg, 0.164 mmol). After 18 h, the reaction mixture was concentrated under reduced pressure and the resulting light yellow oil was subjected to flash chromatography (silica, 1 : 1 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_F 0.5 in 4 : 2.5 : 5.5 v/v/v ethyl acetate/dichloromethane/hexane) afforded compound **11**[15] (198 mg, 90 %) as a clear, colourless oil. $[\alpha]_D$ −60° (*c* 0.4 in methanol). ν_{max} (KBr)/cm^{-1} 2965, 2891, 1732, 1372, 1237, 1125, 1043, 983, 900, 884. δ_H ($CDCl_3$, 500 MHz) 6.19 (m, 1H), 5.62 (m, 2H), 5.50 (s, 1H), 4.68 (m, 1H), 3.97 (d, *J* 6.4, 1H), 3.79 (m, 1H), 2.12 (s, 3H). δ_C ($CDCl_3$, 125 MHz) 170.7 (C), 132.4 (CH), 124.7 (CH), 99.1 (CH), 71.6 (CH), 71.4 (CH_2), 71.3 (CH), 21.0 (CH_3). *m/z* (ESI, +ve) 193 (100 %, $[M + Na]^+$). *m/z* (HRMS ESI (+ve)) 193.0470; $[M + Na]^+$ requires 193.0477.

Compound **12**: A magnetically stirred solution of compound **11** (186 mg, 1.09 mmol) in dichloromethane (20 mL) was treated with *m*-CPBA (980 mg of material of 77 % purity, 4.37 mmol) and anhydrous $NaHCO_3$ (735 mg, 8.75 mmol). After stirring at 18°C for 120 h, the reaction mixture was filtered through a short pad of Celite™ and the filtrate concentrated under reduced pressure. The light yellow residue thus obtained was subjected to flash chromatography (silica, 2 : 1 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions (R_F 0.4 in 8 : 2.5 : 5.5 v/v/v ethyl acetate/dichloromethane/hexane), compound **12**[15] (149 mg, 73 %) as a white, crystalline solid, mp 65–67°C (lit. 68°C[15]). $[\alpha]_D$ −142° (*c* 0.5 in methanol). ν_{max} (KBr)/cm^{-1} 2969, 2899, 1740, 1435, 1372, 1234, 1142, 1055, 981, 904, 882, 821, 802. δ_H ($CDCl_3$, 500 MHz) 5.44 (m, 1H), 4.86 (m, 1H), 4.75 (d, *J* 4.4, 1H), 4.13 (d, *J* 6.3, 1H), 3.89 (m, 1H), 3.16 (m, 1H), 3.01 (m, 1H), 2.15 (s, 3H). δ_C ($CDCl_3$, 125 MHz) 169.8 (C), 97.0 (CH), 69.8 (CH), 67.4 (CH_2), 67.1 (CH), 49.7 (CH), 49.2 (CH), 20.8 (CH_3). *m/z* (ESI, +ve) 209 (100 %, $[M + Na]^+$). *m/z* (HRMS ESI (+ve)) 209.0426; $[M + Na]^+$ requires 209.0426.

Compound **9**: A solution of compound **12** (226 mg, 1.21 mmol) in methanol (10 mL) maintained at 18°C was treated with anhydrous K_2CO_3 (503 mg, 3.64 mmol) and the ensuing mixture stirred magnetically for 2 h then filtered through a short pad of Celite™. The filtrate was concentrated under reduced pressure and the residue subjected to flash chromatography (silica, 2 : 1 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_F 0.4 in 8 : 2.5 : 5.5 v/v/v ethyl acetate/dichloromethane/hexane) afforded compound **9** (168 mg, 96 %) as a white, crystalline solid that was identical, in all aspects, to the material obtained from the conversion **8** → **9** + **10**.

Compound **3**: A solution of compound **9** (466 mg, 3.23 mmol) in dichloromethane (40 mL) was treated with pyridine (2.6 mL, 32.14 mmol) then with DMP (2.06 g, 4.86 mmol) and the resulting solution stirred at 18°C for 18 h before being concentrated under reduced pressure. Subjection of the resulting light yellow oil to flash chromatography (silica, 5 : 4 : 0.5 v/v/v ethyl acetate//hexane/methanol elution) afforded, after concentration of the appropriate fractions (R_F 0.5 in 7 : 2 : 1 v/v/v ethyl acetate/hexane/methanol), compound **3**[17] (449 mg, 98 %) as a white, crystalline solid, mp 95–96°C. $[\alpha]_D$ −193° (*c* 0.5 in methanol). ν_{max} (KBr)/cm^{-1} 2971, 2905, 1744, 1407, 1350, 1140, 1103, 1083, 973, 951, 878, 809. δ_H ($CDCl_3$, 500 MHz) 5.17 (d, *J* 1.9, 1H), 4.99 (m, 1H), 4.04 (d, *J* 7.3, 1H), 3.89 (m, 1H), 3.51 (m, 1H), 3.30 (m, 1H). δ_C ($CDCl_3$, 125 MHz) 192.0 (C), 99.8 (CH), 70.2 (CH), 65.1 (CH_2), 49.9 (CH), 49.1 (CH). *m/z* (EI, 70 eV) 141 (3 %, $[M - H\bullet]^+$), 114 (12), 101 (23), 85 (23), 84 (31), 72 (63), 71 (56), 69 (48), 68 (57), 57 (100). *m/z* (HRMS ESI (+ve)) 141.0188; $[M - H\bullet]^+$ requires 141.0188.

Compounds **13** and **14**: A magnetically stirred solution of compound **3** (122 mg, 0.86 mmol) in methanol (10 mL) maintained at 18°C was treated dropwise with hydrazine (3.4 mL of a 1.0 M THF solution, 3.40 mmol) and after 1 h with acetic acid (250 µL, 4.37 mmol). The ensuing mixture was stirred at 18°C for 24 h then concentrated under reduced pressure and the light yellow oil thus obtained was subjected to flash chromatography (silica, 1 : 1 v/v ethyl acetate/hexane → 6 : 3 : 0.4 v/v/v ethyl acetate/hexane/methanol gradient elution) and thereby affording two fractions, A and B.

Concentration of fraction A (R_F 0.5 in 5 : 4 : 1 v/v/v ethyl acetate/hexane/methanol) gave compound **14**[9] (23 mg, 21 %) as a white, crystalline solid, mp 59–60°C. $[\alpha]_D$ +209° (*c* 0.6 in methanol). ν_{max} (KBr)/cm^{-1} 3390, 2977, 2896, 1640, 1385, 1171, 1096, 1052, 1011, 988, 960, 934, 898, 864, 738, 709. δ_H ($(CD_3)_2CO$, 500 MHz) 6.05 (m, 1H), 5.85 (m, 1H), 5.50 (d, *J* 3.4, 1H), 4.65 (m, 1H), 3.95 (m, 1H), 3.65 (m, 1H), 3.45 (m, 1H), 2.20 (broad s, 1H). δ_C ($(CD_3)_2CO$, 125 MHz) 130.4 (CH), 127.7 (CH), 96.0 (CH), 77.8 (CH), 67.8 (CH), 63.4 (CH_2). *m/z* (ESI, +ve) 151 (100 %, $[M + Na]^+$). *m/z* (HRMS ESI (+ve)) 151.0372; $[M + Na]^+$ requires 151.0371.

Concentration of fraction B (R_F 0.4 in 5 : 4 : 1 v/v/v ethyl acetate/hexane/methanol) gave compound **13**[18] (27 mg, 24 %) as a white, crystalline solid, mp 46–49°C. $[\alpha]_D$ −121° (*c* 0.6 in methanol). ν_{max} (KBr)/cm^{-1} 3413, 2953, 2894, 1449, 1338, 1179, 1097, 985, 896, 866. δ_H ($(CD_3)_2CO$, 500 MHz) 5.37 (s, 1H), 4.35 (m, 1H), 3.82 (m, 2H), 3.63 (m, 1H), 3.58 (broad s, 1H), 1.98–1.83 (complex m, 2H), 1.54–1.48 (complex m, 1H), 1.43–1.37 (complex m, 1H). δ_C ($(CD_3)_2CO$, 125 MHz) 102.1 (CH), 78.3 (CH), 67.2 (CH), 66.8 (CH_2), 28.4 (CH_2), 24.2 (CH_2). *m/z* (ESI, +ve) 153 (100 %, $[M + Na]^+$). *m/z* (HRMS ESI (+ve)) 153.0529; $[M + Na]^+$ requires 153.0528.

Compound **14**: A magnetically stirred solution of compound **3** (178 mg, 1.25 mmol) in methanol (18 mL) was treated dropwise with hydrazine (5 mL of a 1.0 M solution in THF, 5.00 mmol) and after 1 h with acetic acid (430 µL, 7.51 mmol). After a further 2 h, the reaction mixture was concentrated under reduced pressure and the light brown residue subjected to flash chromatography (silica, 2 : 1 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_F 0.5 in 5 : 4 : 1 v/v/v ethyl acetate/hexane/methanol) then gave compound **14**

(72 mg, 45 %) as a white, crystalline solid that was identical in all aspects to the material obtained as described immediately above.

Compound **4**: A magnetically stirred solution of compound **10** (147 mg, 1.02 mmol) in dichloromethane (20 mL) was treated with pyridine (825 mL, 10.20 mmol) then with DMP (649 mg, 1.53 mmol). After 18 h, the reaction mixture was concentrated under reduced pressure and the residue subjected to flash chromatography (silica, 5 : 4 : 0.2 v/v/v ethyl acetate/hexane/methanol elution). Concentration of the relevant fractions (R_F 0.5 in 6 : 3 : 1 v/v/v ethyl acetate/hexane/methanol) afforded compound **4**[17] (143 mg, 99 %) as a white, crystalline solid, mp 71–73°C. $[\alpha]_D$ −48° (*c* 0.5 in methanol). ν_{max} (KBr)/cm^{-1} 2962, 1700, 1416, 1305, 1100, 1063, 914, 873, 803. δ_H ($CDCl_3$, 500 MHz) 5.12 (d, *J* 1.0, 1H), 4.98 (m, 1H), 4.22 (d, *J* 6.4, 1H), 4.01 (m, 1H), 3.70 (m, 1H), 3.28 (m, 1H). δ_C ($CDCl_3$, 125 MHz) 195.4 (C), 100.1 (CH), 73.0 (CH), 64.8 (CH_2), 59.9 (CH), 47.9 (CH). *m/z* (EI, 70 eV) 141 (2 %, $[M - H\bullet]^+$), 114 (8), 101 (18), 72 (49), 71 (84), 69 (58), 57 (100). *m/z* (HRMS (ESI (+ve)) 141.0188; $[M - H\bullet]^+$ requires 141.0188.

Compounds **15** and **16**: A solution of compound **4** (122 mg, 0.86 mmol) in methanol (10 mL) was treated dropwise while being stirred magnetically at 18°C with hydrazine (3.4 mL of a 1.0 M solution in THF, 3.40 mmol). After stirring for a further 1 h, acetic acid (250 μL, 4.367 mmol) was added to the reaction mixture and after a further 24 h, it was concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1 : 1 v/v ethyl acetate/hexane → 2 : 1 v/v ethyl acetate/hexane gradient elution) afforded two fractions, A and B.

Concentration of fraction A (R_F 0.6 in 5 : 4 : 1 v/v/v ethyl acetate/hexane/methanol) afforded compound **16**[5b] (8 mg, 7 %) as a clear, colourless oil. $[\alpha]_D$ −35° (*c* 0.6 in methanol). ν_{max} (KBr)/cm^{-1} 3426, 2975, 2904, 1638, 1376, 1165, 1117, 1080, 1057, 1029, 1008, 979, 957, 902, 854, 718. δ_H ($(CD_3)_2CO$, 500 MHz) 5.80 (m, 1H), 5.68 (m, 1H), 5.41 (d, *J* 2.9, 1H), 4.67 (m, 1H), 4.42 (m, 1H), 4.37 (d, *J* 4.9, 1H), 4.16 (m, 1H), 3.76 (m, 1H). δ_C ($(CD_3)_2CO$, 125 MHz) 131.0 (CH), 128.4 (CH), 96.4 (CH), 76.3 (CH), 68.0 (CH), 62.6 (CH_2). *m/z* (EI, 70 eV) 128 (55 %, $M^{+\bullet}$), 99 (36), 85 (77), 70 (66), 68 (92), 57 (100). *m/z* (HRMS ESI (+ve)) 128.0474; $M^{+\bullet}$ requires 128.0473.

Concentration of fraction B (R_F 0.5 in 5 : 4 : 1 v/v/v ethyl acetate/hexane/methanol) afforded compound **15**[18] (68 mg, 61 %) as a clear, colourless oil. $[\alpha]_D$ −55° (*c* 0.6 in methanol). ν_{max} (KBr)/cm^{-1} 3415, 2956, 2896, 1435, 1335, 1126, 1062, 1033, 991, 933, 875. δ_H ($(CD_3)_2CO$, 500 MHz) 5.33 (s, 1H), 4.25 (t, *J* 4.4, 1H), 4.09 (m, 2H), 3.83 (m, 1H), 3.56 (m, 1H), 1.85–1.79 (complex m, 1H), 1.61–1.51 (complex m, 3H). δ_C ($(CD_3)_2CO$, 125 MHz) 101.1 (CH), 77.1 (CH), 66.6 (CH), 64.8 (CH_2), 31.7 (CH_2), 25.9 (CH_2). *m/z* (ESI, +ve) 153 (78 %, $[M + Na]^+$), 127 (100). *m/z* (HRMS ESI (+ve)) 153.0531; $[M + Na]^+$ requires 153.0528.

Compound **16**: A magnetically stirred solution of compound **4** (98 mg, 0.69 mmol) in methanol (15 mL) maintained at 18°C was treated dropwise with hydrazine (2.8 mL of a 1.0 M solution in THF, 2.80 mmol) and after 1 h with acetic acid (340 μL, 5.94 mmol). After a further 1 h, the reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 2 : 1 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_F 0.6 in 5 : 4 : 1 v/v/v ethyl acetate/hexane/methanol) gave compound **16** (50 mg, 57 %) as a clear, colourless oil that was identical in all aspects to the material obtained as described immediately above.

Compound **2**: A magnetically stirred solution of compound **14** (53 mg, 0.41 mmol) in dichloromethane (25 mL) was treated with molecular sieves (200 mg of 4 Å material) then with manganese dioxide (900 mg, 10.35 mmol). The ensuing mixture was stirred at 18°C for 24 h, then filtered through a short pad of Celite™, and the filtrate concentrated under reduced pressure. Subjection of the ensuing light yellow oil to flash chromatography (silica, 1 : 2 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions (R_F 0.5 in 2 : 2.5 : 5.5 v/v/v ethyl acetate/dichloromethane/hexane), compound **2**[5–7,21] (34 mg, 65 %) as a clear, colourless oil. $[\alpha]_D$ +445° (*c* 1.0 in $CHCl_3$) (lit. +425° (*c* 1.10 in $CHCl_3$)[21b]). ν_{max} (KBr)/cm^{-1} 2965, 2896, 1713, 1694, 1607, 1372, 1251, 1150, 1081, 1026, 970, 937, 891. δ_H ($CDCl_3$, 500 MHz) 7.13 (dd, *J* 9.8, 3.4, 1H), 6.11 (d, *J* 9.8, 1H), 5.81 (d, *J* 3.4, 1H), 4.78 (d, *J* 6.3, 1H), 4.11 (m, 1H), 3.66 (dm, *J* 7.8, 1H). δ_C ($CDCl_3$, 125 MHz) 194.5 (C), 147.3 (CH), 127.1 (CH), 96.1 (CH), 79.6 (CH), 62.7 (CH_2). *m/z* (EI, 70 eV) 126 (93 %, $M^{+\bullet}$), 96 (12), 85 (27), 83 (100), 68 (73), 55 (52). *m/z* (HRMS ESI (+ve)) 126.0316; $M^{+\bullet}$ requires 126.0317.

Using the oxidation protocol described immediately above, compound **16** (82 mg, 0.64 mmol) was also converted into compound **2** (50 mg, 62 %).

X-Ray Crystallographic Studies

Crystallographic Data

Compound **5**, $C_7H_{10}O_4$, *M* 158.15, *T* 200 K, orthorhombic, space group $P2_12_12_1$, *a* 6.6938(2), *b* 9.2713(3), *c* 12.0635(4) Å, *V* 748.66(4) $Å^3$, *Z* 4, D_c 1.403 g cm^{-3}, 1019 unique data ($2\theta_{max}$ 55°), *R* 0.044 (for 894 reflections with $I > 2.0\sigma(I)$), *wR* 0.108 (all data), *S* 0.99.

Compound **9**, $C_6H_8O_4$, *M* 144.13, *T* 150 K, orthorhombic, space group $P2_12_12_1$, *a* 6.4568(1), *b* 9.4927(1), *c* 10.0291(8) Å, *V* 614.71(1) $Å^3$, *Z* 4, D_c 1.557 g cm^{-3}, 1209 unique data ($2\theta_{max}$ 144.8°), *R* 0.021 (for 1204 reflections with $I > 2.0\sigma(I)$), *wR* 0.056 (all data), *S* 1.02.

Compound **10**, $C_6H_8O_4$, *M* 144.13, *T* 150 K, monoclinic, space group $P2_1$, *a* 6.1348(1), *b* 5.1836(1), *c* 9.4057(2) Å, β 93.0546(19)°, *V* 298.68(1) $Å^3$, *Z* 2, D_c 1.602 g cm^{-3}, 939 unique data ($2\theta_{max}$ 144.6°), *R* 0.022 (for 935 reflections with $I > 2.0\sigma(I)$), *wR* 0.061 (all data), *S* 1.02.

Compound **14**, $C_6H_8O_3$, *M* 128.13, *T* 150 K, orthorhombic, space group $P2_12_12_1$, *a* 6.3711(1), *b* 9.5878(1), *c* 9.7015(1) Å, *V* 592.62(1) $Å^3$, *Z* 4, D_c 1.436 g cm^{-3}, 1168 unique data ($2\theta_{max}$ 144.6°), *R* 0.025 (for 1154 reflections with $I > 2.0\sigma(I)$), *wR* 0.064 (all data), *S* 1.03.

Structure Determinations

Images were measured on a Nonius Kappa CCD diffractometer ($Mo_{K\alpha}$, graphite monochromator, λ 0.71073 Å) and data extracted using the *DENZO* package[24] for compound **5**, or an Agilent SuperNova CCD diffractometer ($Cu_{K\alpha}$, mirror monochromator, λ 1.54184 Å) and data extracted using the *CrysAlis PRO* package[25] for compounds **9**, **10**, and **14**. Structure solution was by direct methods (SIR92).[26] The structures of compounds **5**, **9**, **10**, and **14** were refined using the *CRYSTALS* program package.[27] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos 1023960–1023963 for compounds **5**, **9**, **10**, and **14**, respectively). These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or

by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033.

Supplementary Material

The anisotropic displacement ellipsoid plots derived from the single-crystal X-ray structures of compounds **5**, **9**, **10**, and **14** together with the ^{1}H and ^{13}C NMR spectra of compounds **2**–**16** are available on the Journal's website.

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