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Synthesis of (+)-(2*R*,3*S*,4*R*)-2,3,4-trihydroxycyclohexanone from D-glucose

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Abstract—We have described the synthesis of (+)-(2*R*,3*S*,4*R*)-2,3,4-trihydroxycyclohexanone by the reduction of a keto-conduritol derivative, the latter being prepared in five steps from (−)-(2*S*,3*R*,4*S*,5*S*)-2,3,4-tribenzyloxy-5-hydroxycyclohexanone, which is in turn readily synthesized from D-glucose.

Keywords: (+)-(2*R*,3*S*,4*R*)-2,3,4-Trihydroxycyclohexanone; Perbenzylated (−)-keto-conduritol; Conduritol B

1. Introduction

Hydroxycyclohexanes and their derivatives have an important place in biology. Hexahydroxycyclohexanes (inositols) and tetrahydroxycyclohexenes (conduritols) occur naturally and monoketo inositol derivatives (inososes) occur as biosynthetic intermediates in the formation of inositols. *myo*-Inositol 1,4,5-triphosphate is crucially involved in cellular regulation,[1] and inosamines, in which one or two hydroxy groups are replaced by amino groups, are important constituents of some antibiotics.[2] Related compounds are involved in insulin modulation[3] and conduritol derivatives can disrupt glycoprotein processing through site-direct irreversible glycosidase inhibition[4] and represent potential therapeutic agents for treatment of metabolic disorders such as Gaucher's disease, diabetes, cancer and viral infection.[5] As carba-sugars, hydroxycyclohexanes have a methylene group replacing the ring oxygen of normal sugars, and many of this class show interesting biological activity. Therefore, new synthetic procedures, which produce enantiomerically pure representatives of these types of compounds, are of considerable general interest and we now wish to report a convenient synthesis of one such compound, (+)-(2*R*,3*S*,4*R*)-2,3,4-trihydroxycyclohexanone (**1**), a compound in which the spatial disposition of the 2,3,4-hydroxy groups mimics that of the 2,3,4-hydroxy groups in D-glucose. Ketone **1** was prepared by regioselective conversion of (−)-(2*S*,3*R*,4*S*,5*S*)-2,3,4-tribenzyloxy-5-hydroxycyclohexanone (**3**), a compound which may be prepared from D-glucose,[6a] into the perbenzylated (−)-keto-conduritol B (**2**) in five steps, followed by a combined hydrogenation–hydrogenolysis reaction. A retrosynthetic analysis is depicted in Scheme 1.†

2. Discussion

While perbenzylated (+)-(2*S*,3*R*,4*S*)-keto-conduritol (**4**) can be easily prepared by elimination of water from ketone **3**,[6] the synthesis of the (−)-(2*R*,3*S*,4*R*)-enantiomer

† Ketone **1** has previously been obtained[7] by the action of *Acetobacter suboxydans* on 1,4/2,3-cyclohexane-1,2,3,4-tetrol in admixture with (2*S*,3*S*,4*R*)-2,3,4-trihydroxycyclohexanone, from which it was separated by paper chromatography. The latter ketone is the primary product of oxidation and is reversibly transformed into ketone **1** in the ferment medium. However, no physical data for **1** were reported except for its UV spectrum.

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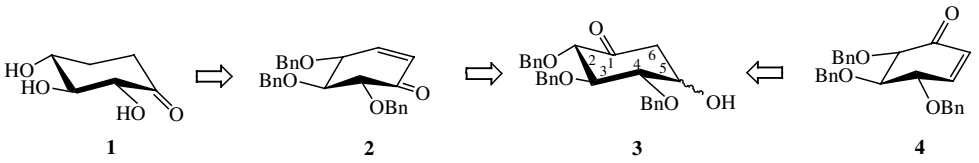
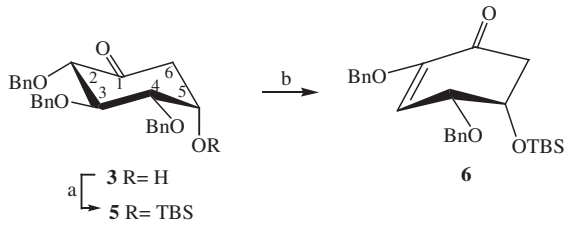


Scheme 1. Retrosynthetic analysis for preparation of cyclohexanone **1** from **3** via the protected (−)-keto-conduritol (**2**).

(**2**) is not so straightforward and requires a regioselective functional group transformation at the C-1 and C-5 positions of compound **3**, with an accompanying change in the position of the double bond, as outlined in Scheme 1.

In our synthesis we prepared the starting material **3** from methyl 2,3,4-tri-*O*-benzyl-6-deoxy-α-D-*xylo*-hex-5-enopyranoside as a 5*S*,5*R* diasteroisomeric mixture (ratio 4:1 determined by ^{1}H NMR integration of CH_2-6 hydrogens), as described by McAuliffe and Stick.[6a] The stereochemistry at C-5 is irrelevant for the proposed synthesis, but we carried out our experiments exclusively with the major 5*S*-isomer to render the NMR spectra more clear, and the formula for **3** in Scheme 2 reflects this fact.

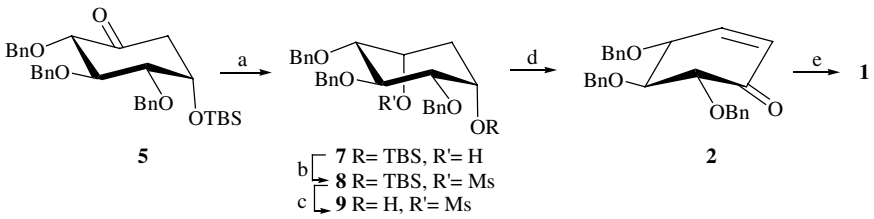
Two different approaches were explored for conversion of compound **3** into (−)-(2*R*,3*S*,4*R*)-2,3,4-tribenzyloxycyclohex-5-enone (**2**). In the first approach we intended to initially convert the carbonyl group of **5** [prepared from **3** in almost quantitative yield by reaction with *tert*-butyldimethylsilyl chloride (TBSCl)] into the corresponding enamine,[8] followed by hydrogenolysis of C–N bond to produce the alkene.[9] It was envisaged that de-*O*-silylation and oxidation would give compound **2**. However, rather surprisingly, piperidine acted exclusively as base on compound **5**, resulting in the elimination of the 3-OBn group, possibly by an E1cb mechanism, and producing the undesired compound **6**, which was characterized on the basis of its spectral properties (Scheme 2). The ^{1}H NMR spectrum of this compound showed the alkene hydrogen H-3 at δ 5.73 (J 5.4 Hz), resonances for H-4, H-5, H-6′, H-6, respectively, centred on δ 4.21, 4.26, 3.04, 2.58 and two sets of signals characteristic of *O*-benzyl groups. The structure of **6** was further confirmed by its ^{13}C NMR spectrum, with a carbonyl and an alkenic carbon at δ 192.09 and 113.75, respectively.



Scheme 2. Reagents and conditions: (a) TBSCl, imidazole, DMF; (b) piperidine.

To circumvent the problem caused by this undesired elimination, the preparation of **2** was investigated by a second approach (Scheme 3). In this modified approach, in which the order of introducing the alkenic function and keto group would be reversed, the carbonyl group would first be reduced in the hope of improving the regioselectivity of the double bond formation.

Contrary to our expectations, neither lithium aluminium hydride nor DIBAL gave satisfactory results on attempted reduction of **5**; partial deprotection of the silylated alcohol or poor product yields resulted. On the other hand, reduction of ketone **5** with sodium borohydride in methanol gave only one product as shown by the fact that only a single set of signals were evident in the ^{13}C spectrum of the alcohol produced (shown by NMR spectroscopy to be **7**—see below) and in subsequent transformation products. That the conformation of **5** is as indicated is supported by the observed coupling constants $J_{2,3}$ 9.2, $J_{3,4}$ 8.5, and $J_{4,5}$ 2.2 Hz, and this places the bulky *tert*-butyldimethylsilyloxy group in β-axial orientation with respect to the carbonyl group. It is well recognized[10] that a bulky group in a cyclohexanone occupying a β-axial position with respect to the carbonyl function leads to 'steric approach control' on carbonyl reduction with sodium borohydride, leading to



Scheme 3. Reagents and conditions: (a) $NaBH_4$, MeOH; (b) MsCl, DMAP, pyridine; (c) water–THF–AcOH; (d) oxalyl chloride, Me_2SO, CH_2Cl_2; (e) cyclohexene–EtOH (2:1), Pd black.

an axial alcohol being produced. The ^{1}H NMR spectrum of the reduction product **7** is in full accord with the structure and conformation shown for this compound, with $J_{1,2}$ 3.3, $J_{2,3}$ and $J_{3,4}$ 9.3, $J_{4,5}$ 2.7, $J_{5,6}$ and $J_{1,6}$ 2.5 and $J_{5,6'}$ and $J_{1,6'}$ 3.7 Hz.

Mesylation of **7** gave the mesylate **8** (87%) as an unstable oil. Hydrolysis of the *O*-silyl protective group of **8** was initially performed under mildly acidic conditions, and this provided product **9** in a reasonable yield (72%), but the reaction was slow. On the other hand, catalytic $Bu_4N^+F^-$ in THF mediated *O*-silyl deprotection of **8** proceeded quite efficiently to furnish alcohol **9** in 85% yield.[11]

Swern oxidation[12] of compound **9** directly produced compound **2** in 73% yield, suggesting that the β-*O*-mesyl group was eliminated during the triethylamine quenching of the oxidation mixture. Compound **2** exhibited $[\alpha]_D$ −64.7, a rotation very similar but opposite in sign to that of the known (+)-isomer. The synthesis of ketone **1** was completed by combined hydrogenation and hydrogenolysis of the protected **2** by hydrogen transfer from cyclohexene, which resulted in simultaneous *O*-benzyl deprotection and double bond reduction, to give the desired product in 86% yield.

3. Experimental

^{1}H NMR spectra were recorded at 300 or 400 MHz on a Bruker DPX300 FT or Bruker DRX 400FT spectrometers, respectively, in $CDCl_3$ unless stated otherwise, with Me_4Si as internal standard. ^{13}C NMR spectra were similarly recorded at 75 or 100 MHz on a Bruker DPX300 FT or Bruker DRX 400FT spectrometers, respectively. Coupling constants (*J* values) are given in Hz. Where appropriate, signal assignments were deduced by DEPT 135, COSY ^{1}H–^{1}H NMR experiments. Optical rotations were measured at ambient temperature with a Schmidt Haensch Polartronic HH8 polarimeter for solns in $CHCl_3$ unless stated otherwise and $[\alpha]_D$ values are given in 10^{-1} deg·cm^2·g^{-1}. IR spectra were recorded on a Nicolet Protégé FT460 spectrophotometer. Low resolution mass spectra and elemental analyses were performed by Mr. A. W. R. Saunders at the University of East Anglia. TLC was performed on silica gel (E. Merck) SIL G-25UV$_{254}$ and compounds on developed plates were detected either by viewing with a UV lamp (254 nm), or by spraying with a 10% sulfuric acid, 1.5% molybdic acid, 1% ceric sulfate spray followed by heating to 150 °C. Column chromatography was performed on Kieselgel 60 (70–230 mm mesh, E. Merck). Where mixed solvents were used, the ratios given are in v/v. Tetrahydrofuran and diethyl ether were pre-dried by storage over sodium wire and obtained anhydrous by distillation from sodium metal and benzophenone once the blue colouration due to the ketyl radical had been achieved; CH_2Cl_2 was obtained anhydrous by distilling from calcium hydride; methanol was dried by distilling from the alkoxide (formed by reaction with activated magnesium) and storage over powdered 3 Å molecular sieves; *N*,*N*-dimethylformamide (DMF) and triethylamine were dried by distilling from calcium hydride immediately prior to use; pyridine was obtained anhydrous by distillation from calcium hydride and storage over potassium hydroxide pellets. Organic solns were dried over anhyd $MgSO_4$. Reactions were maintained at −78 °C by means of a dry ice–acetone bath, and at 0 °C by means of an ice bath.

3.1. (−)-(2*S*,3*R*,4*R*,5*S*)-2,3,4-Tribenzyloxy-5-(*tert*-butyldimethylsilyloxy)cyclohexanone (5)

tert-Butyldimethylsilyl chloride (697 mg; 4.62 mmol) was added to a stirred soln of (−)-(2*S*,3*R*,4*S*,5*S*)-2,3,4-tribenzyloxy-5-hydroxycyclohexanone (**3**) (1.0 g, 2.31 mmol) in DMF (4.6 mL), under argon atmosphere, and imidazole (773 mg, 11.36 mmol) at room temperature and the mixture was allowed to react for 9 h, when monitoring by TLC showed completion. The mixture was then poured into a separatory funnel containing crushed ice, water and diethyl ether. The organic layer thus obtained was washed with brine and then dried and concentrated under diminished pressure. Silica gel chromatography [1:1 EtOAc–hexane] gave **5** as a colourless oil, which solidified (1.25 g, 2.28 mmol, 99%); mp 39.0–41.0 °C; $[\alpha]_D$ −11.4° (*c* 1, CH_2Cl_2). IR (cm^{-1}/film) ν_{max} 1735 (C=O); 1254 [Si(Me)$_2$]; 1107 (SiO); 836 [Si(Me)$_3$]; 777 (SiO). ^{1}H NMR (300 MHz): δ 0.06 (s, 6H, Si(CH_3)$_2$); 0.87 (s, 9H, SiC(CH_3)$_3$); 2.42 (dd, 1H, $J_{6,6'}$ 11.8, $J_{5,6'}$ 2.5 Hz, H-6′); 2.51 (dd, 1H, $J_{5,6}$ 4.1 Hz, H-6); 3.68 (dd, 1H, $J_{4,5}$ 2.2, $J_{3,4}$ 8.5 Hz, H-4); 4.01 (d, 1H, $J_{2,3}$ 9.3 Hz H-2); 4.08 (br t, 1H, H-3); 4.31 (m, 1H, H-5); 4.58, 4.94 (2d, each 1H, J_{AB} 11.7 Hz, PhCH_2O); 4.75 (s, 2H, PhCH_2O), 4.83, 4.88 (2d, each 1H, *J* 10.8 Hz, PhCH_2O) 7.25–7.39 (m, 15H, Ar*H*). ^{13}C NMR (75 MHz): δ −5.09; −4.58 (Si(*C*H$_3$)$_2$); 18.11 (Si*C*(CH$_3$)$_3$); 25.71 (SiC(*C*H$_3$)$_3$); 45.11 (C-6); 67.90 (C-5); 73.11 (Ph*C*H$_2$O); 73.49 (Ph*C*H$_2$O); 75.75 (Ph*C*H$_2$O); 81.89 (C-3); 82.30 (C-4); 85.79 (C-2); 127.67; 127.79; 128.22; 128.38; 128.43 (Ar-*C*); 138.5, 138.3, 138.2 (Ar-*C*q); 203.8 (CO); Anal. Calcd for $C_{33}H_{42}O_5Si$: C, 72.49; H, 7.74. Found: C, 72.46; H, 8.09. *m*/*z* (EI) Found: [M]$^+$ 546.1, $C_{33}H_{42}O_5Si$, requires 546.28.

3.2. (+)-(1*R*,2*R*,3*S*,4*R*,5*S*)-2,3,4-Tribenzyloxy-5-(*tert*-butyldimethylsilyloxy)cyclohexanol (7)

(−)-(2*S*,3*R*,4*R*,5*S*)-2,3,4-Tribenzyloxy-5-(*tert*-butyldimethylsilyloxy)cyclohexanone (**5**) (390 mg, 0.714 mmol) was dissolved in methanol (2 mL) and to the cooled soln (4 °C) $NaBH_4$ (39 mg) was added portionwise. The mixture was stirred for 10 min at 4 °C and then 24 h at

room temperature. TLC [1:4 EtOAc–hexane] indicated the reaction was complete and the soln was concentrated and the mixture was partitioned between water and diethyl ether. The organic phase was separated, the aq layer further extracted with ether, and the combined organic extracts were dried and concentrated under diminished pressure to give a white solid that was chromatographed [1:4 EtOAc–hexane] to yield the compound **7** as a colourless crystals (302 mg, 0.55 mmol, 77%); mp 90.0–92.0 °C; $[\alpha]_D$ +5.2° (*c* 1, CH_2Cl_2). IR (cm^{-1}/film) ν_{max} 3480 (OH). ^1H NMR (300 MHz): δ 0.07 (s, 6H, Si(CH_3)$_2$); 0.89 (s, 9H, SiC(CH_3)$_3$); 1.43 (dt, 1H, $J_{6,6'}$ 14.8, $J_{1,6} = J_{5,6}$ 2.5 Hz, H-6); 2.14 (dt, 1H, $J_{5,6'} = J_{1,6'}$ 3.7 Hz, H-6′); 3.29 (dd, 1H, $J_{4,5}$ 2.7, $J_{3,4}$ 9.3 Hz, H-4); 3.35 (dd, 1H, $J_{1,2}$ 3.3, $J_{2,3}$ 9.3 Hz, H-2); 4.08 (m, 2H, H-5, OH); 4.15 (t, 1H, H-3); 4.26 (m, 1H, H-1); 4.68, 4.77 (2d, each 1H, J_{AB} 11.8 Hz, PhCH_2O); 4.74 (s, 2H, PhCH_2O); 4.85, 4.95 (2d, each 1H, J_{AB} 10.7 Hz, PhCH_2O); 7.24–7.40 (m, 15H, Ar*H*). ^{13}C NMR (75 MHz): δ −4.57, −5.44 (Si(*C*H_3)$_2$); 18.14 (Si*C*(CH$_3$)$_3$); 25.78 (SiC(*C*H_3)$_3$); 33.32 (C-6); 68.62 (C-5); 71.68 (C-1); 72.32 (Ph*C*H$_2$O); 73.78 (Ph*C*H$_2$O); 75.92 (Ph*C*H$_2$O); 79.14 (C-3); 82.59 (C-2); 83.23 (C-4); 127.56, 127.65, 127.66, 127.86, 127.95, 128.05, 128.09, 128.11, 128.13, 128.23, 128.30, 128.32, 128.32, 128.38, 128.41, 128.43 (Ar-*C*); 138.68, 139.07 (Ar-*C*q); Anal. Calcd for $C_{33}H_{44}O_5Si$: C, 72.22; H, 8.08. Found: C, 72.38; H, 8.20. *m*/*z* (EI) Found: $[M]^+$ 548.2, $C_{33}H_{44}O_5Si$, requires 548.30.

3.3. (+)-(1*S*,2*R*,3*R*,4*S*,6*R*)-1,2,3-Tribenzyloxy-4-*tert*-butyldimethylsilyloxy-6-mesyloxycyclohexane (8)

(+)-(1*R*,2*R*,3*S*,4*R*,5*S*)-2,3,4-Tribenzyloxy-5-(*tert*-butyldimethylsilyloxy)cyclohexanol (**7**) (271 mg, 0.49 mmol) was dissolved in pyridine (4.2 mL), and mesyl chloride (0.1 mL; 1.32 mmol) and DMAP (8.4 mg) were added. The mixture was allowed to react for 8 h, when monitoring by TLC [3:7 EtOAc–hexane] showed completion. The reaction was quenched with crushed ice and the product extracted with diethyl ether, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography [3:7 EtOAc–hexane] to give **8** as an oil (269 mg, 0.43 mmol, 87%); $[\alpha]_D$ +3.0° (*c* 1, CH_2Cl_2). IR (cm^{-1}/film): 1352, 1174 (S=O); 900 (S–O). ^1H NMR (300 MHz): δ 0.09 (s, 6H, Si(CH_3)$_2$); 0.94 (s, 9H, SiC(CH_3)$_3$); 1.70 (d, 1H, $J_{5,5'}$ 14.3 Hz, H-5′); 2.38 (d, 1H, H-5); 2.92 (s, 3H, CH_3SO$_2$–); 3.36 (d, 1H, *J* 5.7 Hz, H-3); 3.56 (br s, 1H, H-1); 4.06 (t, 1H, H-2); 4.18 (m, 1H, H-4), 4.65–4.78 (m, 6H, PhCH_2O); 5.13 (br s, 1H, H-6); 7.30–7.36 (m, 15H, Ar*H*). ^{13}C NMR (75 MHz): δ −4.77, −4.88 (Si(*C*H$_3$)$_2$); 18.20 (Si*C*(CH$_3$)$_3$); 25.94 (SiC(*C*H$_3$)$_3$); 33.42 (C-5); 38.79 (*C*H$_3$SO$_2$–); 68.09 (C-4); 73.25 (Ph*C*H$_2$O); 73.70 (Ph*C*H$_2$O); 74.98 (Ph*C*H$_2$O); 77.26 (C-2); 77.40 (C-6); 79.66 (C-1); 81.74 (C-3); 127.56, 127.81, 127.95, 128.33, 128.38, 128.49, 128.52 (Ar-*C*); 138.10, 138.58, 138.88 (Ar-*C*q); Anal. Calcd for $C_{34}H_{46}O_7SSi$: C, 65.14; H, 7.40. Found: C, 65.32; H, 7.62. *m*/*z* (EI) Found: $[M-C_7H_7]^+$ 535.1; $C_{27}H_{39}O_7SSi$, requires 535.22.

3.4. (−)-(1*S*,2*S*,3*R*,4*S*,5*R*)-2,3,4-Tribenzyloxy-5-mesyloxycyclohexanol (9)

Method A: Compound **8** (214 mg; 0.34 mmol) was added to a mixture of 3:1:1 AcOH–water–THF (7.0 mL). After being stirred 8 days at room temperature, the mixture was concentrated and the residue partitioned between water and diethyl ether. The separated aq layer was further extracted with diethyl ether and the combined organic phases were dried, concentrated and the residue was purified by silica gel column chromatography [2:3 EtOAc–hexane] to give the compound **9** as an oil that spontaneously crystallized on storage at 4 °C (126 mg, 0.25 mmol, 72%); mp 161.0–163.0 °C; $[\alpha]_D$ −26.3° (*c* 1, CH_2Cl_2). IR (cm^{-1}/film): 3510 (OH). ^1H NMR (300 MHz): δ 1.63 (dt, 1H, $J_{6,6'}$ 15.0 Hz, H-6′); 2.39 (dt, 1H, $J_{5,6}$ 5.1 Hz, H-6); 2.93 (s, 3H, CH_3SO$_2$–); 3.39 (dd, 1H, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 8.1 Hz, H-2); 3.48 (dd, 1H, $J_{4,5}$ 2.7 Hz, $J_{3,4}$ 8.0 Hz, H-4); 3.95 (t, 1H, H-3); 4.01 (m, 1H, H-1); 4.55, 4.60 (2d, each 1H, *J* 11.7 Hz, PhCH_2O); 4.66 (s, 2H, PhCH_2O); 4.66, 4.72 (2d, each 1H, *J* 11.7 Hz, PhCH_2O); 5.02 (m, 1H, H-5); 7.18–7.28 (15H, m, Ar*H*). ^{13}C NMR (75 MHz): δ 31.41 (C-6); 38.84 (*C*H$_3$SO$_2$–); 66.38 (C-1); 72.60 (Ph*C*H$_2$O); 73.25 (Ph*C*H$_2$O); 75.11 (Ph*C*H$_2$O); 77.27 (C-3, C-5); 78.83 (C-4); 80.72 (C-2); 127.76, 127.81, 127.92, 128.05, 128.14, 128.39, 128.46, 128.49 (Ar-*C*); 137.66, 137.87, 138.26 (Ar-*C*q). Anal. Calcd for $C_{28}H_{32}O_7S$: C, 65.60; H, 6.29. Found: C, 65.90; H, 6.63. *m*/*z* (EI) found: $[M+H_2O]^+$ 530.2; $C_{28}H_{34}O_8S$, requires 530.20.

Method B: A soln of **8** (200 mg, 0.32 mmol) in tetrahydrofuran (4 mL) was treated with 1.0 M soln of tetra-*n*-butylammonium fluoride in tetrahydrofuran (0.15 mL). The reaction mixture was stirred at room temperature for 3 h, when monitoring by TLC [2:3 EtOAc–hexane] showed completion. The soln was dried, concentrated and the residue was subjected to silica gel column chromatography [EtOAc–hexane (2:3)] to give the title compound **9** (138 mg, 0.27 mmol, 85%).

3.5. (−)-(2*R*,3*S*,4*R*)-2,3,4-Tribenzyloxycyclohex-5-enone (2)

A soln of oxalyl chloride (42 mg, 0.03 mL, 0.324 mmol) in CH_2Cl_2 (0.8 mL) was cooled to −78 °C and dimethyl sulfoxide (63 mg, 0.06 mL, 0.803 mmol), in CH_2Cl_2 (0.3 mL) was added dropwise from a syringe over 5 min. The mixture was then stirred for 10 min at −78 °C and then the mesylate **9** (96 mg, 0.187 mmol), dissolved in CH_2Cl_2 (0.3 mL) was added dropwise over 5 min. Stirring was continued at −78 °C for 30 min after which triethylamine (1.6 mL, 11.6 mmol) was added. After 2 h

the cooling bath was removed and water (3.6 mL) was added at room temperature. Stirring was continued for 10 min and the organic layer was then separated. The aq phase was extracted with CH_2Cl_2 (3×5 mL) and the combined organic layers were washed successively with brine (5 mL), 1% aq HCl (5 mL), water (4 mL), 5% aq Na_2CO_3 (5 mL) and water (4 mL). The soln was dried, concentrated and the residue was subjected to silica gel column chromatography [3:7 EtOAc–hexane] to give the title compound **2** as white crystals (57 mg, 0.137 mmol, 73%); mp 61.4–63.0 °C, lit.[6a] 61–62 °C; $[\alpha]_D$ −64.7° (*c* 1, CH_2Cl_2), lit.[6a] for enantiomer $[\alpha]_D$ +64° (*c* 1, CH_2Cl_2). IR (cm^{-1}/film): 1700 (C=O conjugated to C=C), 1610 (C=C). ^1H NMR (300 MHz): δ 3.96 (dd, 1H, $J_{2,3}$ 10.7, $J_{3,4}$ 7.7 Hz, H-3); 4.04 (d, 1H, H-2); 4.36 (dt, 1H, $J_{4,5}$ 2.3 Hz, H-4); 4.73, 4.82 (2d, each 1H, *J* 11.5 Hz, PhCH_2O); 4.74, 5.08 (2d, each 1H, *J* 11.3 Hz, PhCH_2O); 4.80, 4.96 (2d, each 1H, *J* 10.9 Hz, PhCH_2O); 6.03 (dd, 1H, $J_{5,6}$ 10.4, $J_{4,6}$ 2.3 Hz, H-6); 6.80 (dd, 1H, H-5); 7.25–7.44 (15H, m, Ar*H*). ^{13}C NMR (75 MHz): δ 71.74 (Ph*C*H_2O); 72.65 (Ph*C*H_2O); 73.84 (Ph*C*H_2O); 78.88 (C-3); 83.76 (C-4); 84.62 (C-2); 125.99, 126.04, 126.13, 126.25, 126.31, 126.42, 126.60, 126.77 (Ar-C, C-6); 135.84, 136.00, 136.41 (Ar-Cq); 146.29 (C-5); 195.73 (CO); Anal. Calcd for $C_{27}H_{26}O_4$: C, 78.24; H, 6.32. Found: C, 78.14; H, 6.52. *m/z* (EI) Found: $[M-C_7H_7]^+$ 323.1; $C_{20}H_{19}O_4$, requires 323.13.

3.6. (+)-(2*R*,3*S*,4*R*)-2,3,4-Trihydroxycyclohexanone (1)

A soln of (−)-(2*R*, 3*S*,4*R*)-2,3,4-Tribenzyloxycyclohex-5-enone (**2**) (100 mg, 0.24 mmol) in cyclohexene–ethanol (2:1, 7.0 mL) was stirred in the presence of Pd-black catalyst (35 mg) at 80 °C for 4 h, when TLC showed the disappearance of the starting material. The mixture was filtered through a Celite pad and the filtrate was concentrated to afford a solid, which was, washed with diethyl ether and the residue dried under diminished pressure to gave the title compound **1** (30 mg, 0.20 mmol, 86%); $[\alpha]_D$ +4.6° (*c* 0.5, MeOH). IR (cm^{-1}/film): 3380 (OH), 1722 (C=O). ^1H NMR (400 MHz/CD_3OD) δ 1.48 (dddd, 1H, $J_{5,6'}$ 4.5, $J_{4,5}$ 11.3, $J_{5,5'}$ 13.2, $J_{5,6}$ 14.5 Hz, H-5); 2.12 (dddd, 1H, $J_{5',6'}$ 2.8, $J_{5',4}$ 4.8, $J_{5',6}$ 6.1 Hz, H-5′); 2.34 (ddd, 1H, $J_{6,6'}$ 14.5 Hz, H-6′); 2.54 (ddt, 1H, $J_{2,6}$ 1.2 Hz, H-6); 3.25 (dd, 1H, $J_{2,3}$ 9.8, $J_{3,4}$ 9.0 Hz, H-3); 3.81 (ddd, 1H, H-4); 4.04 (dd, 1H, H-2). ^{13}C NMR (100 MHz, CD_3OD) δ 29.97 (C-5); 36.52 (C-6); 72.55 (C-4); 79.43 (C-2); 80.95 (C-3); 209.14 (*C*O). Anal. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.74; H, 7.09.

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References

1. Dalko, P. I.; Sinaÿ, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 773–777.
2. Billington, D. C.; Perron-Sierra, F.; Picard, I.; Beaubras, S.; Duhault, J.; Espinal, J.; Challal, S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2307–2312.
3. Sleight, S.; Wilson, B. A.; Heimark, D. B.; Larner, J. *Biochem. Biophys. Res. Commun.* **2002**, *295*, 561–569.
4. Yu, L.; Cabrera, R.; Ramirez, J.; Malinovskii, V. A.; Brew, K.; Wang, P. G. *Tetrahedron Lett.* **1995**, *36*, 2897–2900.
5. Falshaw, A.; Hart, J. B.; Tyler, P. C. *Carbohydr. Res.* **2000**, *329*, 301–308.
6. (a) McAuliffe, J. C.; Stick, R. V. *Aust. J. Chem.* **1997**, *50*, 193–196; (b) Semeria, D.; Philippe, M.; Delaumeny, J.-M.; Sepulchre, A.-M.; Gero, S. D. *Synthesis* **1983**, 710–713; (c) Miyazaki, H.; Kobayashi, Y.; Shiozaki, M. *J. Org. Chem.* **1995**, *60*, 6103–6109.
7. Posternak, Th.; Reymond, D. *Helv. Chim. Acta* **1955**, *38*, 195–205.
8. Heyl, F. W.; Herr, M. E. *J. Am. Chem. Soc.* **1953**, *75*, 1918–1920.
9. Coulter, J. M.; Lewis, J. W.; Lynch, P. P. *Tetrahedron* **1968**, *24*, 4489–4500.
10. Dauben, W. G.; Fonken, G. J.; Noyce, D. S. *J. Am. Chem. Soc.* **1956**, *78*, 2579–2582.
11. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.
12. Haines, A. H. *Methods for the Oxidation of Organic Compounds, Alcohols, Alcohol Derivatives, Alkyl Halides, Nitroalkanes, Alkyl Azides, Carbonyl Compounds, Hydroxyarenes and Aminoarenes*; Academic Press: London, 1988; p 117.