A simple method for the preparation of 3-hydroxyiminodehydroquinate,† a potent inhibitor of type II dehydroquinase

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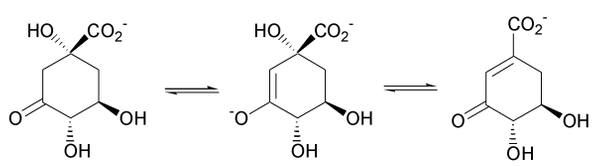
A number of routes to 3-hydroxyiminodehydroquinate **4**, one of the most potent inhibitors of type II dehydroquinase that is currently known, have been investigated. Methods based on the existing literature synthesis, *i.e.* oxime formation of a suitably C-4 and C-5 protected methyl 3-dehydroquinate derivative were initially studied. Benzoyl protection as in **11** did give the desired product but in low overall yield. An alternative BBA protection strategy starting with **7** was successful in generating a C-4/C-5 analogue of the desired oxime **4** in high yield. Further investigation revealed that it was unnecessary to protect the dehydroquinate precursor, hence the potassium salt corresponding to oxime **4** was simply synthesised as a single isomer from methyl dehydroquinate **10**.

Introduction

Types I and II dehydroquinase catalyse the dehydration of 3-dehydroquinate **1** to 3-dehydroshikimate **3**. The type II enzyme operates in the catabolic quinate pathway, thus allowing fungi to use quinic acid as a carbon source (Scheme 1).[1] By contrast,



1 **2** **3**

Scheme 1

both types I and II enzymes are utilised in the shikimate pathway—the biosynthetic pathway by which aromatic amino acids and essential aromatic compounds such as folate and ubiquinone are produced in nature.[2] The shikimate pathway is only present in plants, fungi and bacteria, but not in mammals. A very exciting and recent development is the recognition that the shikimate pathway plays an important role in the apicomplexin parasites such as *Toxoplasma gondii*, *Plasmodium falciparum* (malaria), and *Cryptosporidium parvum*, and that inhibition of the pathway can retard parasitic growth.[3]

These facts, together with the recent determination of crystal structures of the dehydroquinases[4] highlight the need to develop inhibitors of these enzymes as new and novel antibiotic and herbicide leads. One such compound, oxime **4**, has recently been shown to be selective for type II dehydroquinases over type I and to exhibit selectivity amongst the type II enzymes, being more potent against the enzymes from the bacterium *M. tuberculosis* and the fungi *A. nidulans*, than the enzyme from the bacterium *S. coelicolor*.[5] It has been suggested that the type selectivity of **4** is a result of positioning of the oxime functionality into the binding pocket of the type II enzyme that normally[6] stabilises the developing negative charge of a biosynthetic enolate intermediate **2**.[5] By contrast, the type I enzyme operates *via* a mechanism involving the formation of a series of imine–enamine intermediates[7,8] rather than *via* an enolate intermediate. The stabilising effect of the oxime inhibitor is therefore not possible in this case. This potential mechanistic basis for the selectivity and potency of **4** towards the dehydroquinases provides a basis for further inhibitor design. Accordingly, a convenient and reliable method for the synthesis of this deceptively simple molecule, and its analogues, is required.

Oxime **4** has previously been prepared as the sodium salt from quinic acid, in eight steps and 6–9% overall yield.[5] This preparation requires a lengthy and tedious series of protections and deprotections of quinic acid to allow selective functionalisation at C-3.[9] It also gives rise to mixtures of isomers at two key steps which contributes to the low overall yield. Herein we describe an efficient and simple method for the synthesis of this oxime from 3-dehydroquinic acid **6** (Scheme 3). This synthetic route was made possible by our recently published[10] synthesis of **6** from quinic acid **5** (see Scheme 2, 53% overall yield). Analogues with C-4 and C-5 protection have also been prepared (Scheme 3).

Results and discussion

A number of alternative approaches to **4** were investigated (see Scheme 3). Initially, we attempted to simplify the published route by using methyl 3-dehydroquinate bearing a protecting group for the hydroxy groups at C-4 and C-5 as the starting material for the introduction of the oxime functionality at C-3. The butane 2,3-bisacetal (BBA) protected[11] dehydroquinate **7**, available in our laboratory as a precursor to dehydroquinic acid **6**,[10] was simply treated with hydroxylamine hydrochloride in the presence of sodium acetate to afford the oxime **8** in 92% yield and as a single isomer (Scheme 3). The methyl ester of **8** was carefully hydrolysed using sodium hydroxide at room temperature to afford the oxime as the sodium salt **9** which gave satisfactory characterisation data. While this sequence provided access to a useful dehydroquinate-based oxime, it did not allow

† The IUPAC name for 3-hydroxyiminodehydroquinate is (1*S*,4*R*,5*R*)-1,4,5-trihydroxy-3-(hydroxyimino)cyclohexane-1-carboxylate.

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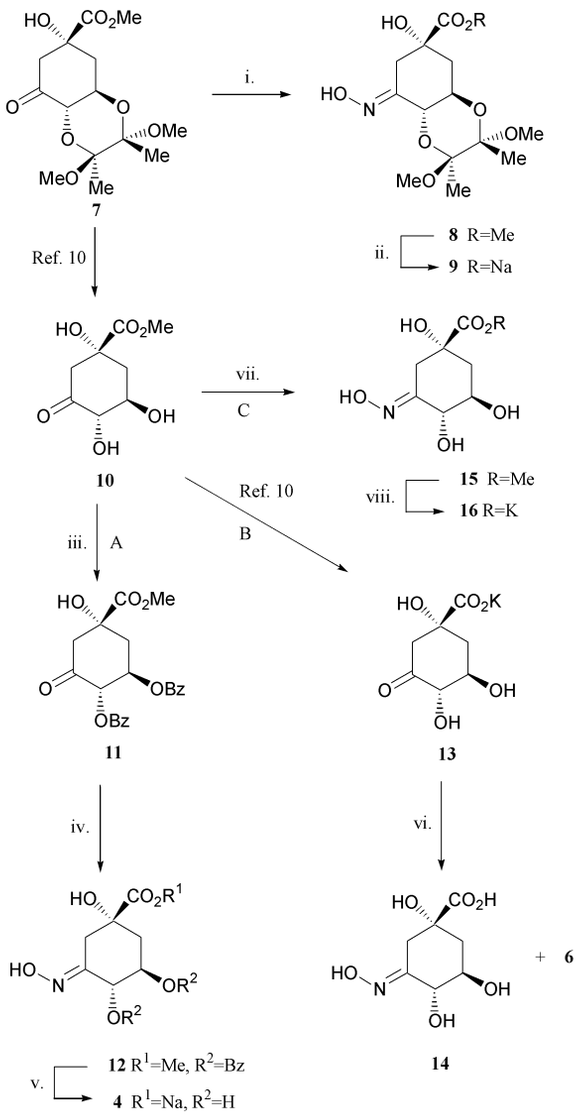
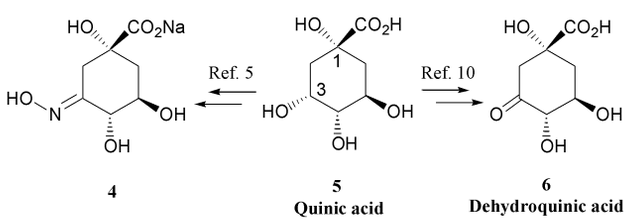


Scheme 2



Scheme 3 i. $H_2NOH{\cdot}HCl$, NaOAc, 92%; ii. NaOH, H_2O, 98%; iii. BzCl, pyridine, 8%; iv. $H_2NOH{\cdot}HCl$, NaOAc; v. NaOH, H_2O; vi. $H_2NOH{\cdot}HCl$; vii. $H_2NOH{\cdot}HCl$, NaOAc, 96%, viii. KOH, H_2O, 97%.

preparation of the desired oxime **4** since the conditions for removing the protecting group are not compatible with the oxime functionality.‡

Next we investigated three routes to the oxime **4** starting from methyl 3-dehydroquinate **10**, itself derived from **7** by deprotection of the BBA group[10] (see A, B and C, Scheme 3). The first of these methods involved protecting the C-4 and C-5 hydroxy groups of **10** with a base-labile protecting group. This alternative to the BBA protection (see **7** above) allows concomitant removal of all protecting groups under conditions that are compatible with the oxime functionality. Consequently, methyl dehydroquinate **10** was treated with pyridine and benzoyl chloride following conditions developed by Mercier *et al.* for the esterification of methyl quinate.[12] The desired dibenzoyl ester **11** was isolated in a low 8% yield after column chromatography and crystallisation.§ A further two fractions were obtained that contained complex mixtures of benzoylated dehydroquinates and dehydroshikimates. Despite the low yield of **11**, a sufficient quantity was obtained to investigate oxime formation. Dehydroquinate **11** was reacted with hydroxylamine hydrochloride and sodium hydroxide to give the oxime **12** which was not purified. This sample was then saponified with sodium hydroxide to give the desired oxime salt **4** in a mixture with sodium benzoate and sodium acetate. Further purification was not attempted since parallel studies using the unprotected dehydroquinates proved more successful.

In the next method, hydrolysis of **10** gave potassium dehydroquinate **13**[10] which was then reacted directly with hydroxylamine hydrochloride. It was thought that the carboxylate functionality of **13** would act as an internal base to liberate free hydroxylamine from its hydrochloride salt and hence minimise the likelihood of forming dehydroshikimate derivatives *via* dehydration at C-1. To this end, **13** was treated with one equivalent of hydroxylamine hydrochloride. The reaction afforded an inseparable mixture of the oxime **14** and dehydroquinic acid **6** (9 : 1 by ^{1}H-NMR). Although it is possible that this reaction could be completed with more careful control of pH, it was thought more expedient to simply perform the saponification after the conversion to the oxime. Hence, in the final and successful method, methyl dehydroquinate **10** was treated with hydroxylamine hydrochloride (1 equiv.) and sodium acetate (1 equiv.). In this case the oxime **15** was obtained as a single isomer (97%) that was fully characterised. The methyl ester of **15** was then carefully hydrolysed using potassium hydroxide to give the desired potassium 3-hydroxyiminodehydroquinate **16** (97%) which gave essentially equivalent data to **4**.[5]

Conclusion

The hydroxyiminodehydroquinate **16** has been synthesised in five steps from quinic acid **5** in 50% yield. A C-4/C-5 analogue **9** has also been prepared in excellent overall yield. The method presented provides a simple and inexpensive route to this important class of dehydroquinase inhibitor.

Experimental

General

^{1}H-NMR spectra were obtained using a Varian Unity 300 NMR spectrometer or a Varian Inova 500 spectrometer at 300 and 500 MHz respectively. ^{13}C-NMR spectra were recorded at a frequency of 75 MHz on a Varian Unity 300 spectrometer. ^{1}H–^{13}C-NMR Correlation experiments were carried out on a Varian Inova 500 spectrometer. Chemical shifts (δ) are given in parts per million (ppm). Mass spectra were recorded on a Kratos MS80RFA instrument for electron impact (EI) technique, or a Micromass LCT spectrometer for the time-of-flight (TOF) method. Infrared spectra were obtained on a Shimadzu Hyper FT-IR instrument. Optical rotations were measured using a Perkin 341 spectrometer. Melting points were taken on an Electrothermal® apparatus and are uncorrected.

Methyl (1*S*,3*E*,4*R*,5*R*)-4,5-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyldioxy)]-1-hydroxy-3-(hydroxyimino)cyclohexane-1-carboxylate 8

To a solution of protected dehydroquinic acid **7**[10] (100 mg, 0.31 mmol) in methanol (1 mL) were added hydroxylamine

‡ Oxime **9** might prove useful for determining the importance of the hydroxy groups at C-4 and C-5 to inhibitory activity.

§ Delfourne *et al.* (see ref. 13) have reported a low 10% yield for the acetylation of methyl dehydroquinate.

hydrochloride (26 mg, 0.37 mmol) and sodium acetate (60 mg, 0.4 mmol) and the mixture was left to stir at room temperature for 15 hours. Methanol was removed under reduced pressure, and the residue was partitioned between ethyl acetate (15 mL) and water (15 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was dried over magnesium sulfate, then concentrated *in vacuo* to afford the oxime **8** as a glass (95 mg, 92%). Mp 117–120 °C; $[\alpha]_D^{20}$ +88.5 (*c* 0.47 in $CHCl_3$) (Found C, 49.06, H, 7.08, N, 3.90, $C_{14}H_{23}O_8N\cdot\frac{1}{2}H_2O$ requires C, 49.10, H, 7.08, N, 4.08%); ν_{max}(KBr)/cm^{-1} 3340, 2954, 1738, 1450, 1379; δ_H ($CDCl_3$, 300 MHz) 1.16 (3H, s, 2′-CH_3 or 3′-CH_3), 1.19 (3H, s, 2′-CH_3 or 3′-CH_3), 1.96 (2H, m, 6-H_2), 2.11 (1H, d, *J* 15, 2-*H*H), 3.16 (3H, s, OCH_3), 3.41 (3H, s, OCH_3), 3.45 (1H, dd, *J* 15, 2, 2-H*H*), 3.72 (3H, s, CO_2CH_3), 4.02 (1H, ddd, *J* 10, 10, 5.5, 5-H), 4.18 (1H, d, *J* 10, 4-H); δ_C ($CDCl_3$, 75 MHz) 17.1 (2′-CH_3 or 3′-CH_3), 17.3 (2′-CH_3 or 3′-CH_3), 32.8 (C-2), 36.8 (C-6), 47.4 (2′-OCH_3 or 3′-OCH_3), 47.7 (2′-OCH_3 or 3′-OCH_3), 52.8 (CO_2CH_3), 67.0 (C-5), 71.3 (C-4), 73.6 (C-1), 99.2 (C-2′ or C-3′), 99.7 (C-2′ or C-3′), 149.5 (C-3), 174.3 (CO_2CH_3); *m*/*z* (EI) 302 ($M^+ - OCH_3$, 7%), 242 (18), 167 (93), 151 (41), 101 (100), 75 (50).

Sodium (1*S*,3*E*,4*R*,5*R*)-4,5-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyldioxy)]-1-hydroxy-3-(hydroxyimino)cyclohexane-1-carboxylate 9

A solution of oxime **8** (300 mg, 0.90 mmol) in diethyl ether (20 mL) was treated with an aqueous solution of sodium hydroxide (2.5 M, 0.65 mL). The reaction mixture was stirred vigorously at room temperature for 5 min. The water was evaporated *in vacuo* to afford the crude product that was recrystallised from ethanol to give oxime **9** as white plates (302 mg, 98%). Mp 122–124 °C; $[\alpha]_D^{20}$ +51.4 (*c* 1.03 in H_2O) (Found C, 39.50, N, 3.25, $C_{13}H_{23}O_8NNa\cdot3H_2O$ requires C, 39.50, N, 3.54%); ν_{max}(KBr)/cm^{-1} 3327, 2949, 1596, 1386, 1130, 1031; δ_H (D_2O, 300 MHz) 1.22 (3H, s, 2′-CH_3 or 3′-CH_3), 1.27 (3H, s, 2′-CH_3 or 3′-CH_3), 1.80 (1H, m, 6-*H*H), 1.90 (1H, dd, *J* 13, 11.5, 6-H*H*), 2.19 (1H, d, *J* 15, 2-*H*H), 3.15 (3H, s, 2′-OCH_3 or 3′-OCH_3), 3.18 (3H, s, 2′-OCH_3 or 3′-OCH_3), 3.24 (1H, dd, *J* 15, 2.5, 2-H*H*), 3.59 (1H, m, 5-H), 4.28 (1H, d, *J* 10.5, 4-H); δ_C (D_2O, 75 MHz) 17.1 (2′-CH_3 or 3′-CH_3), 17.3 (2′-CH_3 or 3′-CH_3), 32.8 (C-2), 36.8 (C-6), 47.4 (2′-OCH_3 or 3′-OCH_3), 47.7 (2′-OCH_3 or 3′-OCH_3), 52.8 (CO_2CH_3), 67.0 (C-5), 71.3 (C-4), 73.6 (C-1), 99.2 (C-2′ or C-3′), 99.7 (C-2′ or C-3′), 149.5 (C-3), 174.3 (CO_2CH_3); *m*/*z* (TOF) found 318.1197, $C_{13}H_{20}O_8N$ requires 318.1189; 318 ($M - Na^+$, 100%), 305 (34).

Methyl (1*R*,4*S*,5*R*)-4,5-bis(benzoyloxy)-1-hydroxy-3-oxocyclohexane-1-carboxylate 11

A solution of methyl dehydroquinate **10**[10] (122 mg, 0.60 mmol) in acetone (1 mL) was cooled to −10 °C and then treated with triethylamine (2 mL). After 5 min, benzoyl chloride (0.28 mL, 330 mg, 2.4 mmol) was added dropwise and the mixture was left to stir for 2 h at which time the reaction was quenched by addition of aqueous hydrochloric acid (0.1 M, 15 mL). The resulting crude mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (50 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The crude mixture was purified by column chromatography using 40% ethyl acetate in petroleum ether to give the dibenzoylated compound **11** as a colourless solid which was recrystallised from diethyl ether (20 mg, 8%). Mp 58–60 °C; $[\alpha]_D^{20}$ −94.8 (*c* 1.8 in CH_2Cl_2) (Found C,64.07, H, 4.89, $C_{22}H_{20}O_8.H_2O$ requires C, 64.07, H, 4.89%); ν_{max}(KBr)/cm^{-1} 3479, 1728, 1600, 1452, 1282, 1253, 1070; δ_H ($CDCl_3$, 300 MHz) 2.55 (1H, m, 6-*H*H), 2.68–2.81 (2H, m, 6-H*H* and 2-*H*H), 3.13 (1H, d, *J* 14, 2-H*H*), 3.85 (3H, s, CO_2CH_3), 5.86–5.97 (2H, m, 4-H and 5-H), 7.35–7.58 (6H, m, ar H × 6), 7.95–8.22 (4H, m, ar H × 4); δ_C ($CDCl_3$, 75 MHz) 38.3 (C-6), 48.6 (C-2), 53.7 (OCH_3), 70.6 (C-5), 73.4 (C-1), 78.9 (C-4), 128.4–133.4 (ar C × 12), 165.3 (4-CO_2Ph or 5-CO_2Ph), 165.7 (4-CO_2Ph or 5-CO_2Ph), 196.6 (C-3).

Sodium (1*S*,3*E*,4*R*,5*R*)-1,4,5-trihydroxy-3-(hydroxyimino)-cyclohexane-1-carboxylate 4

To a solution of triester **11** (120 mg, 0.30 mmol) in water and methanol (1 : 2, 4 mL) were added sodium acetate trihydrate (180 mg, 1.32 mmol) and hydroxylamine hydrochloride (85 mg, 1.22 mmol). The mixture was left to stir overnight at room temperature. The methanol was evaporated under reduced pressure, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic phases were dried over magnesium sulfate, then evaporated *in vacuo* to give the oxime **12** (124 mg) which was not purified further. δ_H ($CDCl_3$, 300 MHz) 2.35 (1H, dd, *J* 13, 11, 6-*H*H), 2.52 (1H, d, *J* 15, 2-*H*H), 2.51–2.58 (1H, m, 6-*H*H), 3.63 (1H, dd, *J* 15, 3, 2-H*H*), 3.82 (3H, s, CO_2CH_3), 5.80 (1H, dt, *J* 10.5, 9.5, 5-H), 5.93 (1H, d, *J* 9.5, 4-H); δ_C ($CDCl_3$, 75 MHz) 33.0 (C-2), 38.1 (C-6), 53.4 (CO_2CH_3), 71.1 (C-5), 72.9 (C-4), 73.3 (C-1), 128.1-133.3 (ar C × 12), 149.9 (C-3), 165.4 (4-CO_2Ph or 5-CO_2Ph), 165.7 (4-CO_2Ph or 5-CO_2Ph), 174.1 (CO_2CH_3); *m*/*z* (TOF) found 428.1345 ($C_{22}H_{21}O_8N$ requires 428.1345), 428 (MH^+, 100%), 413 (25).

A solution of oxime **12** (100 mg, 0.23 mmol) in diethyl ether (2 mL) was treated with an aqueous solution of sodium hydroxide (2.5 M, 0.3 mL, 0.75 mmol) and stirred vigorously for 5 min. The reaction mixture was evaporated to dryness *in vacuo* to give the desired oxime **4** in a mixture with sodium benzoate and sodium acetate as an off-white solid (110 mg, 4.5 : 4.5 : 1 by ^{1}H-NMR). Selected data for oxime **4**:[5] δ_H (D_2O, 300 MHz) 1.90 (2H, m, 6-H_2), 2.12 (1H, d, *J* 15, 2-*H*H), 3.12 (1H, *J* 15, 2, 2-H*H*), 3.66 (1H, ddd, *J* 10, 9, 5.5, 5-H), 3.97 (1H, d, *J* 9, 4-H).

(1*S*,3*E*,4*R*)-1,4,5-Trihydroxy-3-(hydroxyimino)cyclohexane-1-carboxylic acid 14

To a solution of potassium dehydroquinate **13**[10] (122 mg, 0.53 mmol) in water (1 mL) was added hydroxylamine hydrochloride (37 mg, 0.53 mmol) and the mixture was left to stir for 3 h at room temperature. The solvent was removed *in vacuo* to afford an inseparable mixture of the oxime **14** and dehydroquinic acid **6** and potassium chloride as a white hygroscopic solid (155 mg, 9 : 1 by ^{1}H-NMR). Selected data for oxime **14**: ν_{max}(KBr)/cm^{-1} 3400, 1716, 1651, 1226; δ_H (D_2O, 300 MHz) 1.93 (1H, dd, *J* 13.0, 11.5, 6-*H*H), 2.07 (1H, br m, 6-H*H*), 2.24 (1H, d, *J* 14.5, 2-*H*H), 3.30 (1H, dd, *J* 14.5, 1.5, 2-H*H*), 3.69 (1H, br m, 5-H), 4.04 (1H, d, *J* 9.5, 4-H); δ_C (D_2O, 75 MHz) 31.9 (C-2), 39.4 (C-6), 71.1 (C-5), 74.0 (C-1), 74.6 (C-4), 156.4 (C-3), 177.4 (CO_2H). Dehydroquinic acid **6**:[10] δ_H (D_2O, 300 MHz) 2.20 (1H, m, 6-H_2), 2.46 (1H, br d, *J* 14, 2-*H*H), 3.02 (1H, d, *J* 14, 2-H*H*), 3.79 (1H, m, 5-H), 4.18 (1H, d, *J* 9.5, 4-H); δ_C (D_2O, 75 MHz) 39.4 (C-6), 47.6 (C-2), 71.4 (C-5), 74.0 (C-1), 80.6 (C-4), 177.4 (CO_2H), (C-3 not observed).

Methyl (1*S*,3*E*,4*R*,5*R*)-3-(hydroxyimino)-1,4,5-trihydroxycyclohexane-1-carboxylate 15

A solution of methyl dehydroquinate **10**[10] (230 mg, 1.13 mmol) in water (2 mL) was added to sodium acetate trihydrate (153 mg, 1.13 mmol) and hydroxylamine hydrochloride (83 mg, 1.13 mmol). The mixture was left stirring at room temperature for 1.5 h, before it was concentrated under reduced pressure. Methanol (3 mL) was added to the residue, and the insoluble residue of sodium chloride was filtered off over Celite. The filtrate was evaporated under reduced pressure to give a thick oil which was dried under high vacuum to afford the oxime **15** as a very hygroscopic white solid (250 mg, 96%). Mp 99–100 °C;

$[\alpha]_D^{20}$ −25.5 (*c* 1.06 in MeOH) (Found C, 43.08, H, 6.01, N, 6.02, $C_8H_{13}O_6N\cdot{}^1\!/_4H_2O$ requires C, 42.94, H, 6.08, N, 6.25%); ν_{max}(KBr)/cm^{-1} 3415, 2856, 2341, 1732, 1633, 1373, 1087; δ_H (acetone-d_6, 500 MHz) 1.88 (1H, m, 6-*H*H), 2.10 (1H, ddd, *J* 13.5, 5, 2.5, 6-H*H*), 2.24 (1H, d, *J* 15, 2-*H*H), 3.32 (1H, dd, *J* 15, 2.5, 2-*H*H), 3.70 (3H, s, CO_2CH_3), 3.76 (1H, ddd, *J* 11, 9, 5, 5-H), 4.08 (1H, d, *J* 9, 4-H); δ_C (D_2O, 75 MHz) 32.1 (C-2), 40.1 (C-6), 52.1 (CO_2CH_3), 71.9 (C-5), 74.1 (C-4), 78.5 (C-1), 154.0 (C-3), 174.8 (CO_2CH_3); *m*/*z* (TOF) found 220.0821, $C_8H_{14}NO$ requires 220.0821; 220 (MH^+, 100).

Potassium (1*S*,3*E*,4*R*,5*R*)-1,4,5-trihydroxy-3-(hydroxyimino)-cyclohexane-1-carboxylate 16

A solution of the methyl ester **15** (115 mg, 0.52 mmol) in water (2 mL) was cooled to 0 °C and then treated with a solution of potassium hydroxide (29.2 mg, 0.52 mmol) in water (1.2 mL). The ice bath was removed and the mixture was left stirring and warming to room temperature for 5 min. The mixture was then concentrated under reduced pressure to give the desired potassium salt of the oxime **16** as a pale yellow hygroscopic glass (122 mg, 97%). $[\alpha]_D^{20}$ −40.3 (*c* 1.0, H_2O); δ_H (D_2O, 500 MHz) 1.93 (1H, dd, *J* 13.5, 10.5, 6-*H*H), 2.0 (1H, ddd, *J* 13.5, 5, 2.5, 6-H*H*), 2.23 (1H, d, *J* 14.5, 2-*H*H), 3.22 (1H, dd, *J* 14.5, 2.5, 2-H*H*), 3.72 (1H, ddd, *J* 10.5, 9.5, 5, 5-H), 4.07 (1H, d, *J* 9.5, 4-H); δ_C (D_2O, 75 MHz) 32.8 (C-2), 40.2 (C-6), 71.8 (C-5), 74.9 (C-4), 75.3 (C-1), 157.3 (C-3), 180.5 (CO_2K); *m*/*z* (TOF) found 204.0508, $C_7H_{10}O_6N$ requires 204.0508; 204 (M − K^+, 100%), 186 (22), 126.9 (59).

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