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Stereocontrolled synthesis of the aconitine D ring from D-glucose†

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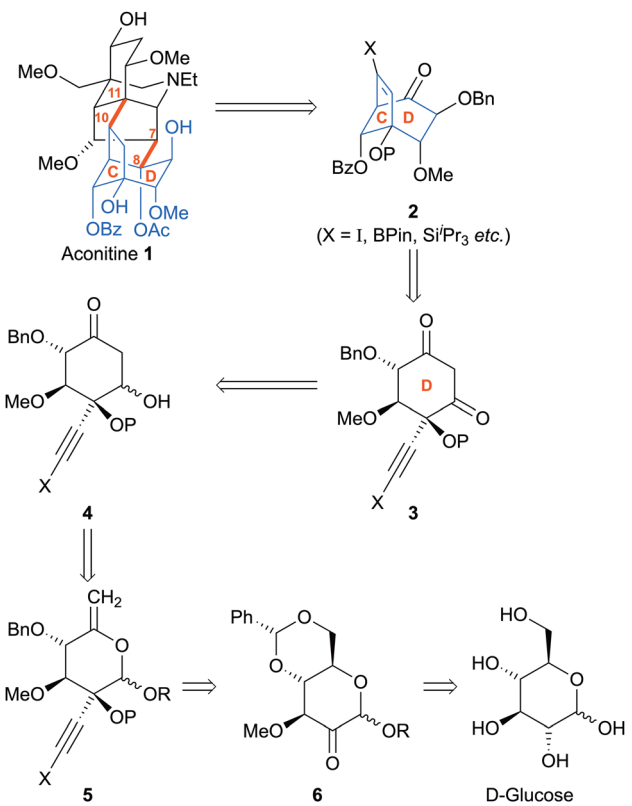
The synthesis of a fully oxygenated aconitine D ring precursor from D-(+)-glucose is described. The route features a highly diastereoselective alkynyl Grignard ketone addition and a base-mediated enelactone to 1,3-diketone rearrangement.

Introduction

Aconitine **1**, a C_{19} norditerpenoid alkaloid isolated from plants of the genus *Aconitum*,[1] is a potent neurotoxin that exerts its principal pharmacological effect by binding to and activating voltage-gated Na^+ channels.[2] Its poisonous properties have gained a certain literary notoriety, featuring in the works of authors as diverse as Ovid, Shakespeare, and Arthur Conan Doyle.[3] Related diterpenoid alkaloids display significant antagonist activity at the nicotinic acetylcholine receptor[4] and cytotoxicity.[5] The densely functionalized cage structure, containing 15 stereogenic centres, has attracted interest from the synthetic chemistry community.[6] Despite landmark syntheses of simpler related compounds,[7] no total synthesis of aconitine has yet been reported, perhaps a reflection of additional stereochemical complexity present throughout the molecule, particularly concentrated in ring D where all six ring atoms are stereogenic centres.[8] A retrosynthetic strategy predicated upon disconnections across the C(7)–C(8) and C(10)–C(11) bonds back to a CD subunit (Scheme 1) is appealingly convergent, and has been elegantly showcased by Gin[7b] and Reisman[9] in their respective syntheses of neofinaconitine and talatisamine. Noting that five of the six aconitine D ring stereocentres bear oxygen substituents, we envisioned assembly of this key subunit in enantiomerically pure form from a carbohydrate precursor, by exploiting the potential for Ferrier carbocyclisation[10] to convert a pyranose-derived enol ether such as **5** to the corresponding cyclohexanone **4**. The additional two carbons necessary to construct the C-ring could then be supplied by addition of an alkynyl metal to ketone **6**, setting the stage for ring C closure *via* Conia-ene intramolecular diketone alkynylation.[11] Given that an alkynyl iodide (*cf.* **3**, X = I) has been shown to be a competent reactant in this type of cyclisation,[11a] the potential to access vinyl halide **2** (or an organometallic derivative thereof)



Scheme 1 Retrosynthetic plan.

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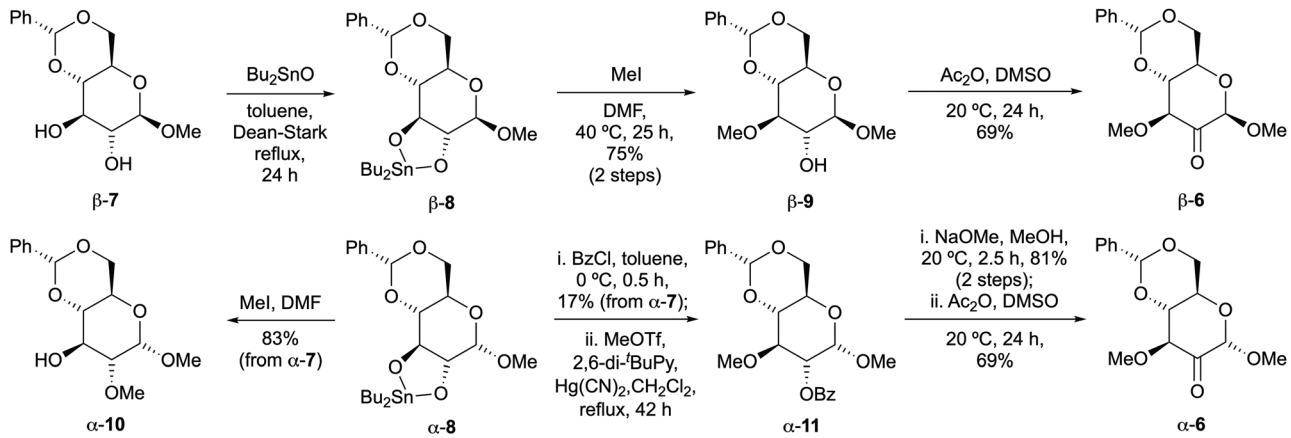
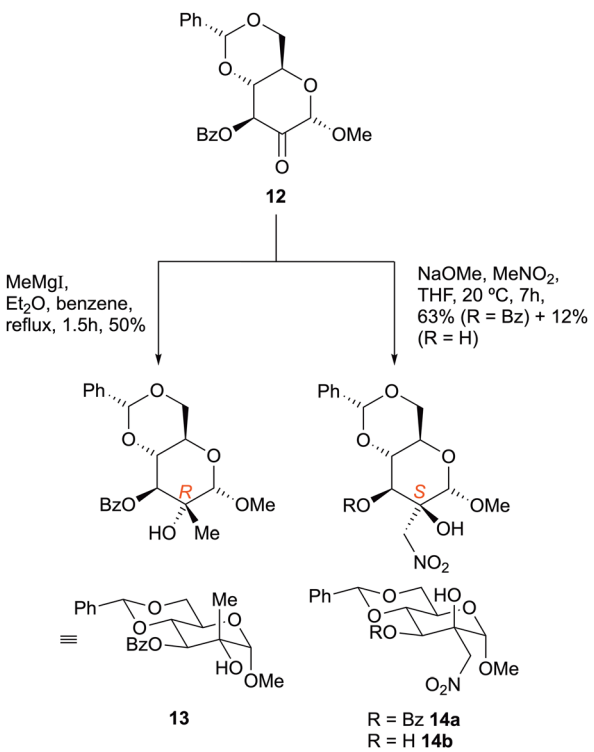
†Electronic supplementary information (ESI) available: Full experimental details and characterisation data for novel compounds, X-ray crystallographic data and NMR spectra. CCDC 2343856. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4ob00561a



Scheme 2 Preparation of ketoglycosides α-6 and β-6.

and elaborate it towards the target *via* cross-coupling is apparent. Benzylidene acetal **6** (R = Me) is an attractive substrate given the rigidity imparted by the *trans*-fused bicyclic scaffold; moreover, selective reduction of the acetal[12] would maintain a protecting group on the 2° alcohol whilst revealing the 1° alcohol *en route* to enol **5**.

Towards the realization of this concept, we report here a stereocontrolled synthesis of diketone **3** (X = Si^iPr_3; P = Bn) from D-(+)-glucose as a platform for further synthetic studies towards **1**.

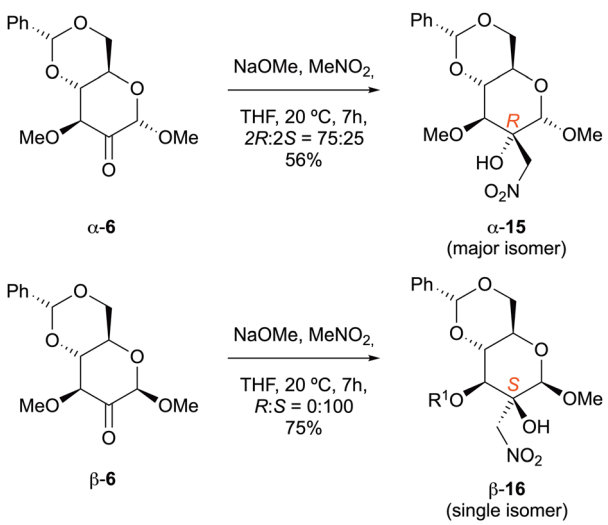


Scheme 3 Stereochemical outcomes of nucleophilic additions to ketone 12 (Mikami & Shin).[14]

Results and discussion

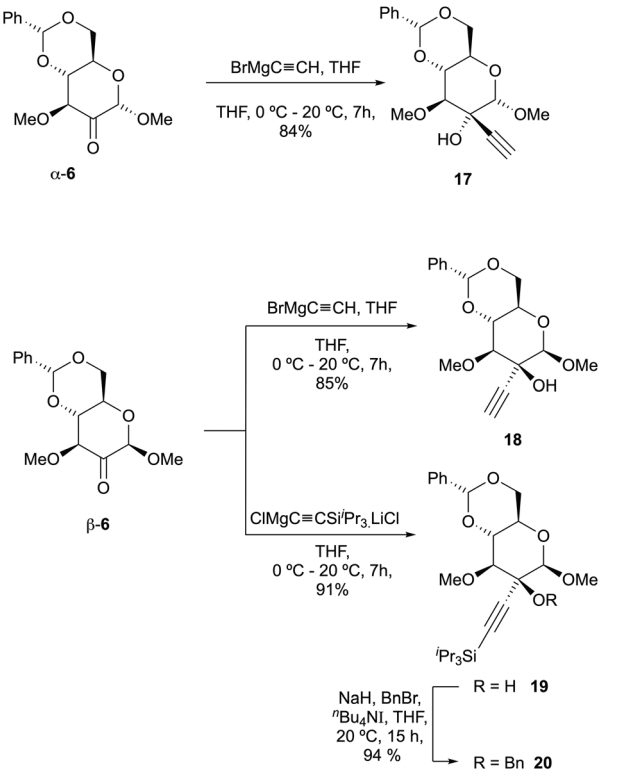
From the outset we recognized that the configuration at the anomeric centre of **6** would influence the stereochemical outcome of nucleophilic attack at the adjacent ketone. Treatment of stannylene acetal β-**8** (from benzylidene acetal β-**7**)[13] with methyl iodide gave high selectivity for 2° alcohol β-**9**, whereupon oxidation under Albright–Goldman conditions delivered the desired 3-OMe isomer β-**6** (Scheme 2). On the other hand, methylation of α-**8** took place selectively at the 2-position (giving α-**10**), requiring temporary protection of the 2-hydroxyl group as a benzoate ester to access α-**6** *via* α-**11** as described by Fuchs.[14]

With both α-**6** and β-**6** in hand we turned our attention to the installation of the alkyne moiety at C(2). Mikami and Shin reported that whereas addition of methyl magnesium iodide to analogous ketone **12** proceeded *via* exclu-



Scheme 4 Addition of nitromethane to α-6 and β-6.

sive axial attack to give **13**, nitromethane gave the product of equatorial attack **14** (Scheme 3).[15] As the latter outcome would set the correct configuration and install a group



Scheme 5 Addition of alkynyl Grignards to α-6 and β-6.

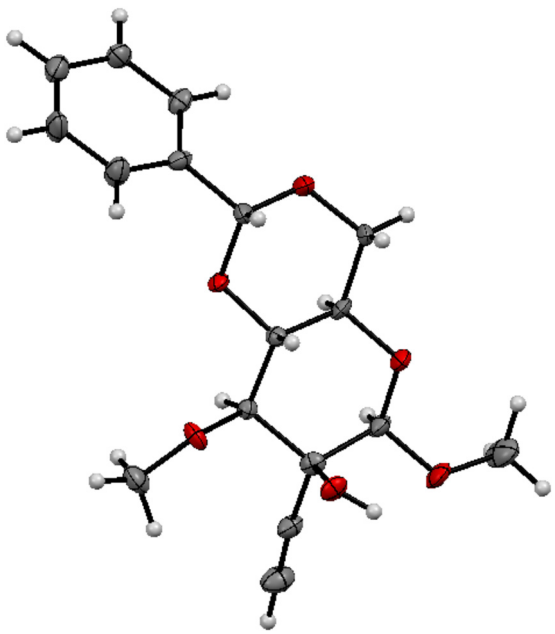
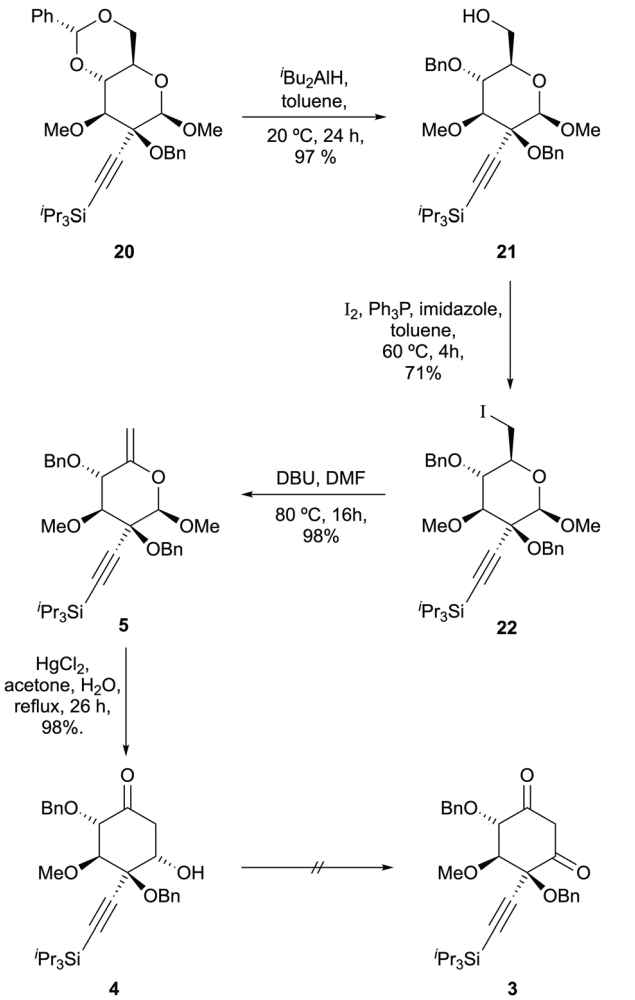
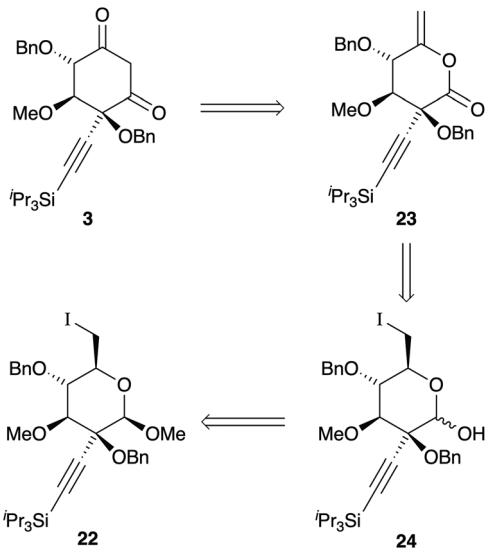


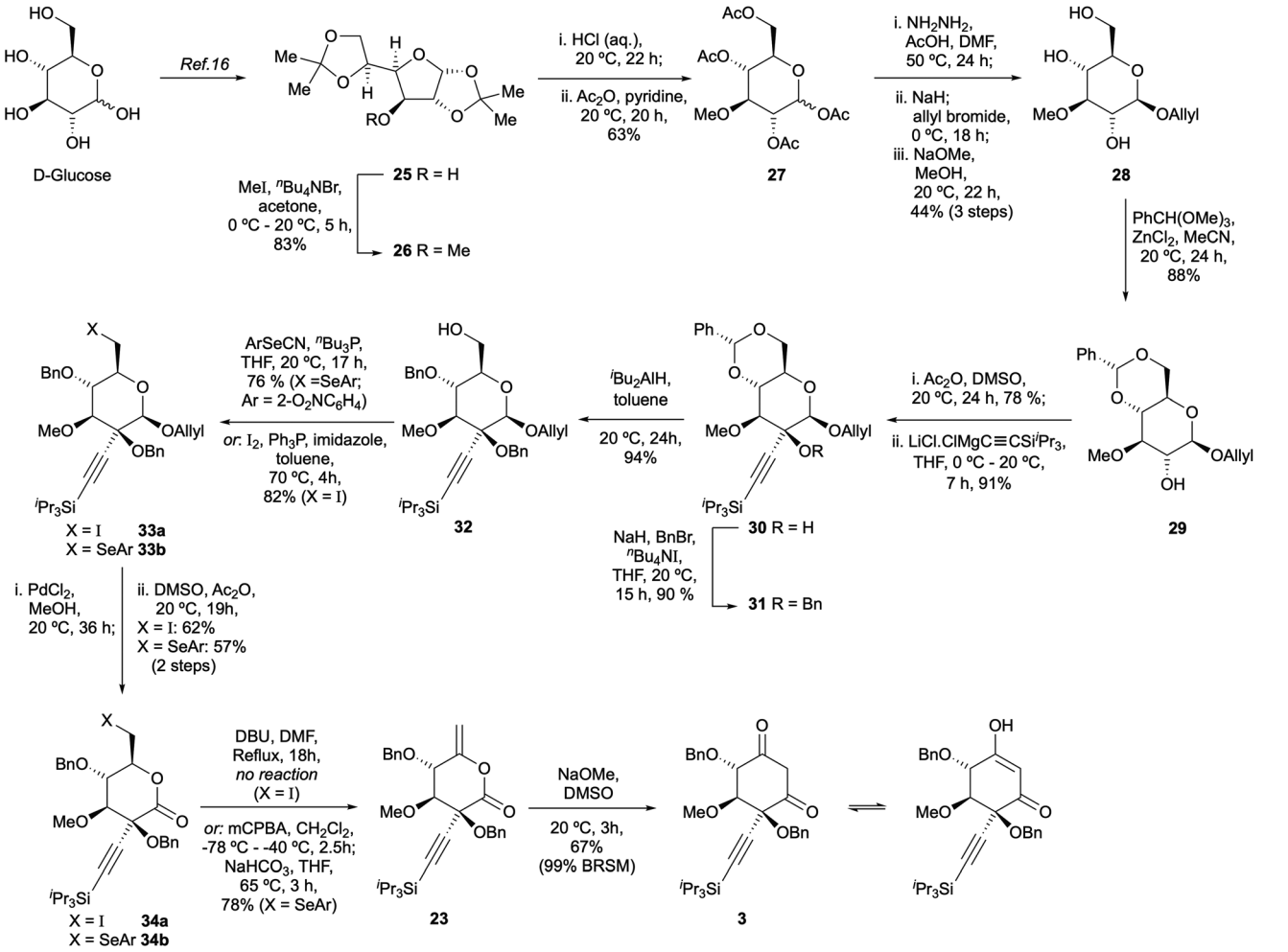
Fig. 1 ORTEP representation of compound 18 (thermal ellipsoids at 30% probability).



Scheme 6 Preparation of β-hydroxyketone 4 from glucopyranoside 20 *via* Ferrier carbocyclisation.



Scheme 7 Revised retrosynthesis.



Scheme 8 Synthesis of aconitine D ring precursor 3 from D-glucose.

capable of manipulation to the alkynyl group of **4**, we reacted α-**6** with nitromethane under the same conditions but obtained an inseparable mixture of diastereomeric products enriched in the undesired (2*R*)-isomer **15** (Scheme 4). Under the same conditions, β-**6** did give the desired product of equatorial attack **16** as a single stereoisomer, but we were unable to elaborate this intermediate further towards the target.

The high selectivity for equatorial attack on β-**6** prompted us to examine addition of alkynyl metals to these substrates. We were delighted to observe complete selectivity for axial attack of bromomagnesium acetylide upon α-**6**, giving **17** in 84% yield; moreover, the desired product of equatorial attack was obtained as a single diastereomer by exposing β-**6** to the same reagent, giving **18** in 85% yield (Scheme 5). These results parallel those of Miljković for sodium borohydride-mediated reduction of these substrates and may be rationalised by minimisation of dipole–dipole interactions in an early transition state.[16]

The relative configuration of these compounds was tentatively assigned with the aid of NOE studies‡ and confirmed for compound **18** by single crystal X-ray diffractometry (Fig. 1). Unsurprisingly, attempted reductive cleavage of the benzylidene acetal of **18** using di-isobutyl aluminium hydride (DIBALH) resulted in hydroalumination of the alkyne, necessitating installation of protecting groups at both the alcohol and alkyne terminus. This was accomplished by treating β-**6** with triisopropylsilylalkynylmagnesium chloride and benzylating the resultant 3° alcohol **19** to give **20** (Scheme 5). Treatment of **20** with DIBALH in toluene[12] afforded 1° alcohol **21** with complete regioselectivity and no evidence of alkyne reduction. Base-induced elimination of iodide **22** (obtained from alcohol **21** *via* an Appel reaction) gave enol

‡The NOESY spectrum for compound **17** displayed a cross-peak corresponding to an interaction between 2-OH and axial 3-H, whereas for compound **18**, a cross-peak for 2-OH and axial 4-H was observed. For compound **16**, a cross-peak for 2-OH and axial 4-H was also observed, along with one between axial 3-H and one CH_2NO_2 proton. NOESY spectra of compound **20** and other 2-OBn compounds evidenced interaction between the CH_2Ph protons and the $-Si^iPr_3$ group but not 4-H, suggesting that these compounds adopt a conformation where the bulky benzyl group is oriented away from the tetrahydropyran ring.

ether **5** (Scheme 6). Gratifyingly, upon exposure to mercury(II) chloride, **5** underwent Ferrier carbocyclisation to give cyclohexanone **4** in 98% yield as a single diastereomer.§ The stereoselectivity observed is in line with that observed by Machado and rationalized by a chelated chair-like transition state.[17] A wide range of oxidising agents and conditions was surveyed in an effort to convert **4** to diketone **3**, but without success. We therefore considered the possibility that the correct oxidation state at this carbon could be set earlier in the synthesis, envisioning that diketone **3** might be derived directly by rearrangement of enelactone **23**,[18] accessible in turn from **22** *via* selective *O*-demethylation and oxidation of lactol **24** (Scheme 7).

Unfortunately, we were unable to identify conditions to selectively 1-*O*-demethylate either **21** or **22**. A second-generation route was therefore developed, where the refractory methyl group was replaced with an allyl group. However, this apparently minor structural change resulted in a reversal in *O*-methylation regioselectivity (*cf.* Scheme 2), so a more fundamental route redesign was carried out. To circumvent reliance on the capricious stannylene acetal chemistry, 1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranose **25** (preparable from D-glucose in a single step)[19] was chosen as a starting point. Methylation of the single exposed hydroxyl group gave **26**,[20] which was converted to tetraacetate **27**, obtained as an inconsequential 85 : 15 mixture of anomers in 63% overall yield. Selective de-acetylation of **27** at the anomeric position with hydrazine,[21] followed by treatment with base and allyl bromide[22] generated an 87 : 13 (β : α) ratio of epimeric allyl glycosides, from which the desired β-anomer **28** was isolated in 44% unoptimised yield following methanolysis of the remaining acetate groups. Benzylidene acetal formation gave 2° alcohol **29**. Oxidation, alkynyl Grignard addition, and 3° alcohol protection paralleled the methyl glycoside series, giving **30**; pleasingly, complete stereoselectivity for equatorial addition to the ketone was also observed (Scheme 8). Following DIBALH reduction of the benzylidene acetal, alcohol **32** was converted to iodide **33a**. Palladium-catalyzed deallylation[23] and hemiacetal oxidation proceeded smoothly to give lactone **34a** in 62% yield; however, base-induced elimination of HI was unsuccessful. Alcohol **32** was therefore converted to selenide **33b** using Grieco's protocol[24] and processed along the same lines to give lactone **34b**. Oxidation of the selenide[25] triggered spontaneous elimination to give the desired enelactone **23**, which upon treatment with sodium methoxide rearranged cleanly to diketone **3**, isolated as a mixture of diketone and ketoenol isomers in 67% yield (Scheme 8).

§ The ^{1}H NMR coupling constants for 2-H [δ_H 4.31 (d, J = 12.0 Hz)] and 3-H [δ_H 3.85 (d, J = 12.0 Hz)] of compound **4** suggest that both these protons are axially disposed, whereas that of 5-H [δ_H 4.10 (t, J = 2.8 Hz)] represents coupling to 6-H$_{eq}$ [δ_H 2.49 (dd, J = 14.5, 2.8 Hz)] and 6-H$_{ax}$ [δ_H 2.85 (dd, J = 14.5, 2.8 Hz)] with a J value typical of an equatorial proton.

Conclusions

The synthesis of diketone **3** from 1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranose **25** (one step from glucose) was accomplished in 14 steps and 2.5% overall yield (3.9% BRSM). The route features a highly stereoselective alkynyl Grignard addition to a ketopyranose controlled by the configuration at the anomeric centre, and an unusual enelactone to diketone rearrangement. Compound **3** represents a promising staging post in the proposed approach to aconitine, given that β-dicarbonyl moieties have been profitably employed by Toste as the nucleophilic component in gold-catalysed Conia-ene cyclisations (including a 5-*endo-dig* process to furnish a [3.2.1]-bridged product),[11a] and replacement of the triisopropylsilyl group with a more tractable iodine substituent is feasible with either alkyne (**3**) or alkene (**2**) substrates.[26] Moreover, the product of such a reaction would contain carbonyl groups of different reactivity: the ketone embedded in the more strained 5-membered ring would be expected to exhibit greater reactivity towards reducing agents, rendering compound **2** (Scheme 1) potentially accessible *via* this strategy. Efforts in our laboratory are currently focused on applying these transformations to generate enantiopure CD building blocks as the foundation of a convergent approach to aconitine itself.

Author contributions

JD and IAP carried out all synthetic experimental work under the supervision of DMG and JBS. X-ray crystallography was carried out and analysed by CRR. DMG conceived the ideas and wrote the manuscript. DMG, JD and IAP conceived and designed the reactions. All authors edited and approved the final manuscript.

Conflicts of interest

There are no conflicts to declare.

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