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Practical, Multigram Preparation of Synthetically Useful, Enantiomerically Pure Building-Blocks from Quinic Acid

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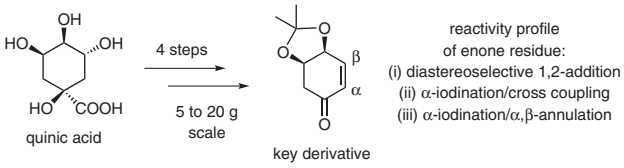

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Abstract The naturally abundant, enantiomerically pure cyclitol quinic acid has been converted into a synthetically useful enone in nearly quantitative yield using the operationally straightforward and reproducible protocols reported herein. The latter compound, which was obtained in multigram quantities, engages in a diastereoselective 1,2-addition reaction with a hydrazone-based nucleophile. Furthermore, a readily derived α-iodoenone participates in both cross-coupling and α,β-annulation reactions. The results reported here emphasize that the now practically accessible cyclohexenones are useful, enantiomerically pure building blocks for organic synthesis.

Key Words 1,2-addition, α,β-annulation, cross-coupling, cyclohexenone, enantiomerically pure, α-iodination, quinic acid

Quinic acid (**1**, Figure 1), a naturally occurring, abundant and enantiomerically pure cyclitol, has been cleverly deployed in numerous synthetic endeavours.[1] Common derivatives associated with these studies have included the enone **2**[2] and, to a lesser extent, its α-iodinated counterpart **3**.[2c–f]

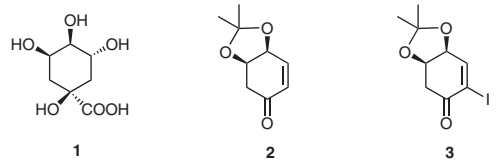
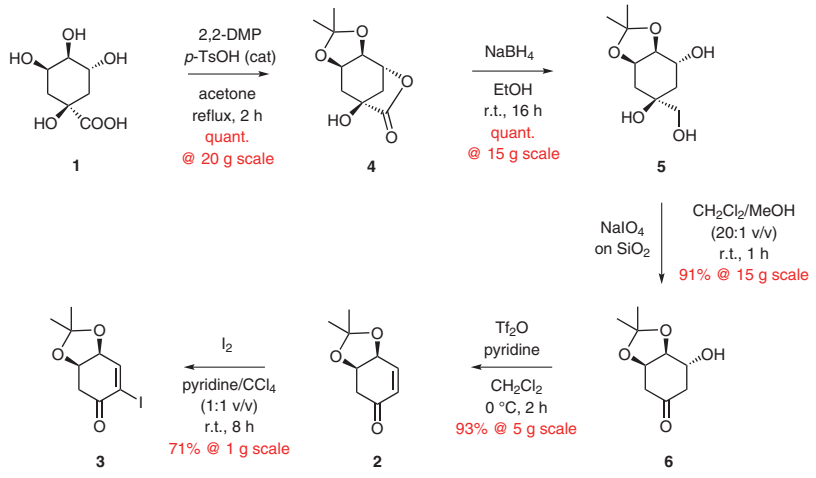


Figure 1 The structures of quinic acid (**1**) and its two known derivatives **2** and **3**

During studies exploiting enantiomerically pure cyclohexanoids[3] as starting materials for the preparation of biologically active natural products, we required multigram quantities of compounds **2** and **3**. However, while following the reported procedures for this purpose, we encountered various problems. These included the previously noted[4] lack of reproducibility of key transformations and difficulties associated with certain isolation and purification regimes. Consequently, we developed and report herein modifications to these procedures that have allowed reproducible, highly efficient access to compounds **2** and **3** in multigram quantities. We also report some new reactions of these compounds that serve to further emphasize their significant synthetic utility.

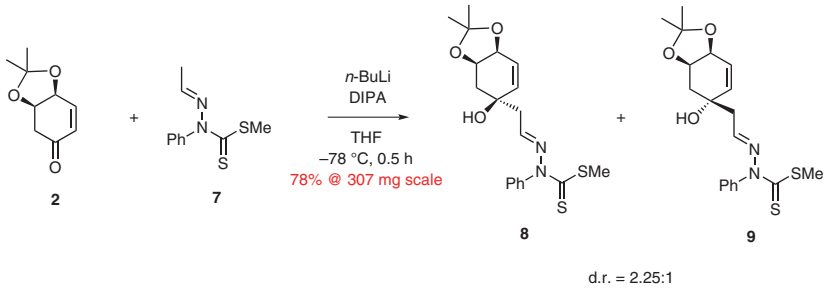
The reaction sequence used to obtain enantiomerically pure enone **2** and its iodinated counterpart **3** is shown in Scheme 1. It begins with the quantitative conversion of quinic acid (**1**) into the known lactone **4** on a 20-gram scale using modifications to previously reported conditions.[2,5] Amongst the various reagents and conditions described for the reductive cleavage of compound **4** leading to triol **5**,[2,5] sodium borohydride in ethanol at ambient temperatures proved most effective and gave the product in quantitative yield on a 15-gram scale. While we were unable to purify this triol following reported methods,[2b] we found that simply passing a solution of the concentrated reaction mixture in 2:1 v/v dichloromethane/methanol through a short pad of flash chromatography-grade silica gel delivered the compound in nearly pure form. The oxidative cleavage of compound **5** proved particularly problematic and our attempts to effect this conversion using a reported[2a] procedure involving an aqueous buffer solution led to lower than 10% yields of the target ketone **6**. These difficulties were overcome by using silica gel-supported sodium metaperiodate[2g,6] in dichloromethane/methanol at ambient temperatures, which delivered ketone **6** in 91% yield on a 15 g scale.



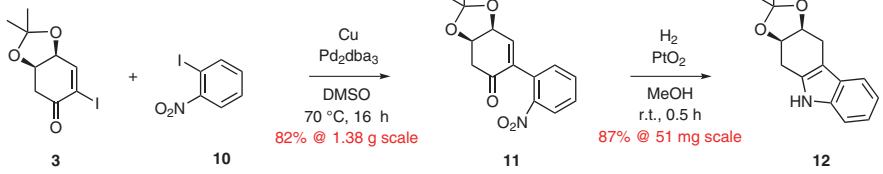
Scheme 1 The synthetic route used to obtain compounds **2** and **3**

Dehydration of compound **6** to generate the target enone **2** also proved problematic because of the ease with which a competing two-fold elimination reaction could occur that delivered hydroquinone. Eventually, and based on observations gleaned from a related study,[7] we established that treatment of β-hydroxyketone **6** with triflic anhydride and pyridine in dichloromethane at 0 °C gave the desired enone **2** in 93% yield on a 5 g scale. This reaction presumably proceeds via *in situ* formation and then E1cB-type elimination of the derived sulfonic acid ester, evidence for which was fleetingly suggested by TLC analysis of the reaction mixture. All the spectroscopic data obtained on compound **2** matched those reported previously as well as the assigned structure.[2] Notably, despite being a crystalline solid, this enone was rather unstable. In one instance, for example, it was found to decompose over a period of seven days when stored under nitrogen at 0 °C. The α-iodination of compound **2** was best accomplished using the Johnson protocol[8] and when this was carried out on a gram scale, product **3** was obtained in 71% yield. Again, all the spectroscopic data acquired on this compound matched those reported previously.[2c] Relative to the parent enone **2**, the iodinated derivative was found to be stable under a broader range of chemical and thermal conditions.

Acquisition of compounds **2** and **3** on the scales defined above allowed us to further explore their chemical properties, which we did in a way that was complementary to prior studies.[2] Accordingly, compound **2** was reacted with the anion derived from hydrazone **7**[9a] at –78 °C to deliver a 2.25:1 mixture of the epimeric 1,2-addition products **8** and **9** in 78% combined yield (Scheme 2). Each of these chromatographically separable adducts was characterised individually. A subsequent single-crystal X-ray analysis (see the experimental section and the SI for details) established that the major diastereomer arose from preferential α-face addition of the anion to enone **2**, and we attributed this selectivity to the partial blocking effect of the associated β-oriented acetonide residue. The $^{13}C\{^1H\}$ NMR spectra of compounds **8** and **9** are distinctive because the one derived from the former displays 17 signals while the latter gives rise to 19. We attributed this difference to the restricted rotation of the phenyl residue in epimer **9** which results from its position on the *endo*-face of the bicyclic core of the compound. We are currently investigating whether adducts **8** and **9**, as well as certain derivatives, can engage in radical cyclisation reactions[9] that provide access to enantiomerically pure perhydroindoles. Results will be reported in due course.



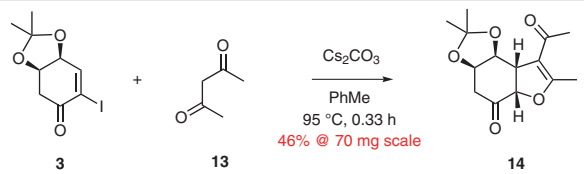
Scheme 2 The reaction of enone **2** with the anion derived from hydrazone **7**



Scheme 3 The cross-coupling of α-iodoenone **3** with *o*-iodonitrobenzene (**10**)

We also investigated whether iodoenone **3** could participate in cross-coupling reactions. Thus, compound **3** was subjected to a palladium-catalysed Ullmann cross-coupling reaction[10] with *o*-iodonitrobenzene (**10**) and the anticipated product **11** was formed in 82% yield on a 1.38 g scale (Scheme 3). While attempts to effect the reductive cyclisation[10] of compound **11** using hydrogen and Pd on C only led to complex mixtures (presumably due to the acidity of the catalyst), PtO_2 delivered the enantiomerically pure tetrahydrocarbazole **12** in 87% yield. A single crystal of the *N*-hydroxy derivative of compound **12** was isolated from the crude reaction mixture associated with this reduction and subjected to X-ray analysis.[11] Details are given in the experimental section and the SI.

Maycock and co-workers have synthesised ring-fused aziridines by treating compound **3** with certain anilines.[2c,d] Based on this and our own observation[12] that simple α-iodoenones can act as bis-electrophiles in annulation reactions, we examined whether compound **3** could engage in analogous processes with bis-nucleophiles. Specifically, when compound **3** was reacted with pentane-1,3-dione (**13**) in the presence of caesium carbonate at 95 °C, the tetrahydrobenzofuran **14** formed rapidly and as a single diastereoisomer, albeit in just 46% yield (Scheme 4). The illustrated stereochemistry of product **14** was confirmed via single-crystal analysis (see the experimental section and the SI for details). This configuration presumably results from selective 1,4-addition of the anion derived from diketone **13** to the less hindered α-face of the Michael acceptor **3**. Attempts to prepare cyclopropanated derivatives of compound **3** via its reaction with nitromethane or diethyl malonate[12] under a variety of conditions failed to deliver the desired products. In each instance, the only major products of reaction were those resulting from fragmentation/aromatization of substrate **3**.



Scheme 4 Reaction of compound **3** with pentane-1,3-dione (**13**) leading to annulation product **14**

The results reported here build on those of others[2] and serve to emphasize that the now practically accessible and enantiomerically pure cyclohexenones **2** and **3** are versatile building blocks that can, under carefully controlled conditions, engage in diverse chemical transformations.[13] This is particularly notable because of the otherwise observed tendency of these compounds to aromatize under both acidic and basic conditions.

(3a*R*,4*R*,7*S*,8a*R*)-7-Hydroxy-2,2-dimethyltetrahydro-4,7-methano[1,3]dioxolo[4,5-*c*]oxepin-6(4*H*)-one (4)

A magnetically stirred solution of quinic acid (**1**) (20.0 g, 104.1 mmol, 1.0 equiv), 2,2-dimethoxypropane (51 mL, 416 mmol, 4.0 equiv) and *p*-TsOH (1.98 g, 10.4 mmol, 0.1 equiv) in acetone (300 mL) was heated under reflux for 2 h. The cooled reaction mixture was quenched with triethylamine (4.33 mL, 31.2 mmol, 0.3 equiv) and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:3 → 1:1 v/v EtOAc/petroleum spirit gradient elution) to afford, after concentration of the relevant fractions (R_f = 0.3, 1:1 v/v EtOAc/petroleum spirit), lactone **4** (22.30 g, quant.) as a white powder.

Alternative purification procedure: The concentrated, crude reaction mixture was dissolved in EtOAc (*ca.* 50 mL) and the resulting solution was filtered through a short pad of flash chromatography-grade silica gel contained in a sintered-glass funnel. The pad was washed with additional EtOAc (*ca.* 200 mL) and the filtrate was concentrated under reduced pressure. The residue thus obtained was dissolved in 1:2 v/v EtOAc/petroleum spirit (*ca.* 100 mL) at 60 °C, and the resulting solution was left to stand overnight at ambient temperatures. This afforded crystals of lactone **4** which were isolated by decanting off the mother liquor and washing the residual solid with small quantities of 1:3 v/v EtOAc/petroleum spirit.

Mp 142–144 °C (lit.[5] 143–144 °C); $[\alpha]_D$ –35.1 (*c* = 1.0, CH_2Cl_2) (lit.[5] –34.46 (*c* = 1.6, $CHCl_3$)).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.71 (dd, *J* = 6.1, 2.6 Hz, 1 H), 4.49 (m, 1 H), 4.29 (m, 1 H), 3.10 (s, 1 H), 2.63 (d, *J* = 11.8 Hz, 1 H), 2.36 (m, 1 H), 2.30 (m, 1 H), 2.17 (dd, *J* = 11.8, 2.9 Hz, 1 H), 1.51 (s, 3 H), 1.32 (s, 3 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 178.9, 109.8, 75.8, 72.1, 71.50, 71.48, 38.1, 34.2, 26.9, 24.3.

IR: 3425, 2983, 2932, 1773, 1074 cm^{-1}.

(3a*S*,4*R*,6*R*,7a*R*)-6-(Hydroxymethyl)-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxole-4,6-diol (5)

A magnetically stirred solution of lactone **4** (14.72 g, 68.7 mmol, 1.0 equiv) in absolute EtOH (150 mL) maintained at 0 °C was treated, in one portion, with $NaBH_4$ (9.10 g, 240.49 mmol, 3.5 equiv). After stirring the ensuing mixture at ambient temperatures for 16 h, brine (50

mL) was added and stirring was continued for a further 16 h. The resulting mixture was concentrated under reduced pressure and the residue was redissolved in 1:2 v/v methanol/dichloromethane (*ca.* 50 mL). The ensuing mixture was filtered through a short pad of flash chromatography-grade silica contained in a sintered-glass funnel, which was subsequently washed with methanol/dichloromethane (*ca.* 200 mL of a 1:3 v/v mixture). The filtrate was concentrated under reduced pressure to afford the title triol **5** (15.0 g, quant.) as a clear gum (R_f = 0.6 in 1:3 v/v methanol/dichloromethane).

Mp 113–114 °C (lit.[5] 117–117.5 °C); $[\alpha]_D$ –45.9 (*c* = 1.0, EtOH) (lit.[5] –56.07 (*c* = 1.4, MeOH))

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.49 (m, 1 H), 4.09 (m, 1 H), 3.97 (t, *J* = 5.9 Hz, 1 H), 3.48 (d, *J* = 10.7 Hz, 1 H), 3.40 (d, *J* = 10.7 Hz, 1 H), 3.22 (br s, 1 H), 2.52 (br s, 1 H), 2.35 (br s, 1 H), 2.36 (dt, *J* = 15.7, 2.5 Hz, 1 H), 2.00 (m, 1 H), 1.85 (dd, *J* = 15.7, 3.8 Hz, 1 H), 1.54 (s, 3 H), 1.49 (dd, *J* = 13.7, 10.2 Hz, 1 H), 1.37 (s, 3 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 109.1, 80.2, 74.2, 72.5, 70.2, 68.9, 38.2, 33.0, 28.2, 25.6

IR: 3358, 2935, 1643, 1373, 1218, 1044 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{18}O_5$·Na: 241.1052; found: 241.1045

(3a*R*,7*R*,7a*S*)-7-Hydroxy-2,2-dimethyltetrahydrobenzo[*d*][1,3]dioxol-5(4*H*)-one (6)

A magnetically stirred solution of triol **5** (15.0 g, 68.7 mmol, 1.0 equiv) in dichloromethane/methanol (250 mL of a 20:1 v/v mixture) was treated, at ambient temperatures, with freshly prepared, silica-supported $NaIO_4$ (90 g, ca. 1.5 g/mmol of substrate – prepared as described below*). After 1 h, the reaction mixture was filtered through a sintered-glass funnel packed with a small layer of sand. The ensuing silica/sand pad was washed with dichloromethane/methanol (*ca.* 300 mL of a 20:1 v/v mixture) and the combined filtrates were concentrated under reduced pressure to afford alcohol **6** (12.8 g, quant.) as a white, crystalline solid (R_f = 0.3 in 1:1 v/v EtOAc/petroleum spirit).

* The required silica-supported $NaIO_4$ was prepared using minor modifications to a published procedure.[6] Thus, a solution of $NaIO_4$ (20 g) in distilled water (45 mL) was heated to 70–80 °C and poured, while hot, onto flash chromatography-grade silica (90 g) contained in a vessel large enough to permit vigorous agitation by hand. The material was agitated until an even, smoothly flowing powder was obtained.

Mp 70 °C (lit.[2a] 80–81 °C); $[\alpha]_D$ +138.0 (*c* = 1.0, CH_2Cl_2) (lit.[2a] +141.24 (*c* = 0.89, $CHCl_3$)).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 4.70 (m, 1 H), 4.30 (dt, *J* = 7.1, 2.3 Hz, 1 H), 4.22 (m, 1 H), 2.80 (dd, *J* = 17.6, 3.7 Hz, 1 H), 2.65 (dm, *J* = 17.6 Hz, 2 H), 2.44 (dm, *J* = 17.6 Hz, 1 H), 1.43 (s, 3 H), 1.35 (s, 3 H) (signal due to OH group proton not observed).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 208.3, 108.7, 74.9, 72.2, 68.0, 41.6, 40.1, 26.3, 23.8

IR: 3412, 2988, 2917, 1708, 1210, 1047 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{14}O_4$·Na: 209.07890; found: 209.0787.

(3a*R*,7a*S*)-2,2-Dimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxol-5(4*H*)-one (2)

A magnetically stirred solution of β-hydroxyketone **6** (5.00 g, 26.9 mmol, 1.0 equiv) in anhydrous dichloromethane (50 mL) was cooled to 0 °C and treated, dropwise, with pyridine (7.60 mL, 94 mmol, 3.5 equiv) followed by triflic anhydride (5.00 mL, 29.5 mmol, 1.1 equiv). The ensuing mixture was stirred at 0 °C for 2 h before being poured onto water (50 mL). The separated aqueous phase was extracted with dichloromethane (3 × 30 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The brown residue thus obtained was subjected to flash chromatography (silica, 3:7 v/v EtOAc/petroleum spirit elution). Concentration of the relevant fractions (R_f = 0.4) afforded enone **2** (4.18 g, 93%) as a clear, colorless liquid that solidified upon standing below 4 °C.

$[\alpha]_D$ +140.1 (*c* = 1.0, EtOH) (lit.[2a] +147.5 (*c* = 0.48, $CHCl_3$)).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.60 (m, 1 H), 5.98 (m, 1 H), 4.68 (m, 1 H), 4.64 (m, 1 H), 2.87 (m, 1 H), 2.65 (dd, *J* = 17.6, 4.0 Hz, 1 H), 1.34 (s, 3 H), 1.33 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 195.3, 145.8, 128.7, 109.8, 73.3, 70.9, 38.6, 27.7, 26.5.

IR: 2987, 2918, 1679, 1369, 1222, 1051, 845 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{14}O_4$·Na: 191.0684; found: 191.0678.

(3a*R*,7a*S*)-6-Iodo-2,2-dimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxol-5(4*H*)-one (3)

A magnetically stirred solution of enone **2** (1.00 g, 5.95 mmol, 1.0 equiv) in CCl_4/pyridine (10.0 mL of a 1:1 v/v mixture) was cooled to 0 °C and treated, in small portions over 0.2 h, with molecular iodine (3.77 g, 14.86 mmol, 2.5 equiv). The ensuing reaction mixture was warmed to ambient temperatures and stirred for a further 8 h. Sodium metabisulfite (50 mL of a 1:9 w/v aqueous solution) was then poured into the reaction mixture and the separated aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with brine (50 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. Subjection of the ensuing light-brown oil to flash chromatography (silica, 1:9 v/v EtOAc/petroleum spirit elution) afforded, after concentration of the relevant fractions (R_f = 0.4 in 3:7 v/v EtOAc/petroleum spirit), the title α-iodoenone **3** (1.24 g, 71%) as a light-tan, crystalline solid.

Mp 62–64 °C (lit.[2c] 63–65 °C); $[\alpha]_D$ –68.4 (*c* = 1.0, EtOH) (lit.[2c] –78.6 (*c* = 0.72, CH_2Cl_2)).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.42 (br s, 1 H), 4.60 (m, 2 H), 3.21 (d, *J* = 17.3 Hz, 1 H), 2.80 (d, *J* = 17.3 Hz, 1 H), 1.38 (s, 6 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 188.4, 154.4, 110.5, 104.4, 73.6, 73.5, 37.3, 27.7, 26.5.

IR: 2986, 2932, 1691, 1224, 1059 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* [M+MeOH+Na]$^+$ calcd for $C_9H_{11}IO_3$·CH_3OH·Na: 348.9913; found: 348.9910.

Methyl (*E*)-2-(2-((3a*R*,5*S*,7a*S*)-5-Hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*]-[1,3]dioxol-5-yl)ethylidene)-1-phenylhydrazine-1-carbodithioate (8) and Methyl (*E*)-2-(2-((3a*R*,5*R*,7a*S*)-5-Hydroxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-yl)ethylidene)-1-phenylhydrazine-1-carbodithioate (9)

A magnetically stirred solution of diisopropylamine (DIPA) (847 µL, 6.02 mmol, 3.3 equiv) in anhydrous THF (5.0 mL) maintained under a nitrogen atmosphere was cooled to –78 °C then treated with *n*-butyllithium (1.6 M in hexanes, 3.42 mL, 5.48 mmol, 3.0 equiv). After 1 h, a solution of hydrazone **7**[9a] (1.23 g, 5.48 mmol, 3.0 equiv) in anhydrous THF (3.0 mL) was added dropwise and the resulting, orange-colored mixture was stirred for a further 1 h at –78 °C. Subsequently, a solution of enone **2** (307 mg, 1.83 mmol, 1.0 equiv) in anhydrous THF (4.0 mL) was added, and the reaction mixture was stirred for a further 0.5 h before being quenched, at –78 °C, with NH_4Cl (3.0 mL of a saturated aqueous solution). The separated aqueous phase was extracted with

EtOAc (3 × 5 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing residue was subjected to flash chromatography (silica, 1:3 → 1:1 v/v EtOAc/petroleum spirit gradient elution) to afford three fractions, A–C.

Concentration of fraction A (R_f = 0.9 in 1:3 v/v EtOAc/petroleum spirit) afforded the unreacted hydrazone **7** (779 mg, 63% recovery) as an orange oil that solidified upon standing below 4 °C. This material was identical to an authentic sample.[9a]

Concentration of fraction B (R_f = 0.5 in 1:3 v/v EtOAc/petroleum spirit) afforded compound **8** (384 mg, 54%) as a light-yellow, microcrystalline solid.

Mp 100–101 °C; $[\alpha]_D$ +62.3 (*c* = 1.0, EtOH).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.53 (m, 2 H), 7.45 (m, 1 H), 7.14 (d, *J* = 7.0 Hz, 2 H), 6.84 (t, *J* = 5.8 Hz, 1 H), 5.73 (d, *J* = 10.2 Hz, 1 H), 5.63 (ddd, *J* = 10.2, 2.9, 1.4 Hz, 1 H), 4.49 (m, 1 H), 4.47 (m, 1 H), 3.58 (br s, 1 H), 2.59 (s, 3 H), 2.53 (dd, *J* = 14.3, 5.5 Hz, 1 H), 2.47 (dd, *J* = 14.3, 6.2 Hz, 1 H), 2.19 (m, 1 H), 1.96 (dd, *J* = 15.0, 2.3 Hz, 1 H), 1.41 (s, 3 H), 1.34 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 202.0, 145.6, 139.1, 133.0, 130.3, 129.4, 128.7, 126.8, 109.7, 72.9, 71.8, 67.5, 44.0, 35.5, 28.0, 26.4, 18.9.

IR: 3510, 2984, 2918, 1382, 1324, 1217, 1070, 1039, 701 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{25}N_2O_3S_2$: 393.1306; found: 393.1294.

Concentration of fraction C (R_f = 0.3 in 1:3 v/v EtOAc/petroleum spirit) afforded compound **9** (171 mg, 24%) as a viscous, dark-yellow oil.

$[\alpha]_D$ –0.6 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.54 (m, 2 H), 7.46 (m, 1 H), 7.16 (d, *J* = 7.1 Hz, 2 H), 6.81 (t, *J* = 4.6 Hz, 1 H), 5.93 (d, *J* = 10.3 Hz, 1 H), 5.63 (dd, *J* = 10.3, 3.2 Hz, 1 H), 4.51–4.47 (complex m, 2 H), 3.63 (br s, 1 H), 2.74 (dd, *J* = 16.6, 4.8 Hz, 1 H), 2.67 (dd, *J* = 16.6, 4.4 Hz, 1 H), 2.59 (s, 3 H), 2.15 (dd, *J* = 14.5, 5.2 Hz, 1 H), 1.99 (dd, *J* = 14.5, 3.8 Hz, 1 H), 1.39 (s, 3 H), 1.34 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 201.6, 149.5, 145.9, 138.5, 134.7, 130.3, 129.6, 128.9, 126.3, 116.0, 108.8, 71.8, 70.8, 69.1, 43.1, 38.0, 27.6, 25.7, 18.9.

IR: 3380, 2983, 2919, 1381, 1323, 1215, 1070, 1039, 699 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{25}N_2O_3S_2$: 393.1306; found: 393.1296.

(3a*R*,7a*S*)-2,2-Dimethyl-6-(2-nitrophenyl)-3a,7a-dihydrobenzo[*d*][1,3]dioxol-5(4*H*)-one (11)

A magnetically stirred mixture of iodide **3** (1.38 g, 4.69 mmol, 1.0 equiv), copper powder (1.47 g, 23.5 mmol, 5.0 equiv [freshly activated via sonication in a 0.02 M aqueous ethylenediaminetetraacetic acid solution]), $Pd_2(dba)_3$ (215 mg, 0.24 mmol, 0.05 equiv) and *o*-iodonitrobenzene (2.34 g, 9.39 mmol, 2.0 equiv) in anhydrous DMSO (85 mL) was heated at 70 °C for 16 h before being cooled and filtered through a pad of diatomaceous earth. The filtrate was diluted with dichloromethane (50 mL) and then washed with NH_4Cl (50 mL of a saturated aqueous solution), water (50 mL) and brine (50 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. Subjection of the ensuing oil to flash chromatography (silica, 3:7 v/v EtOAc/petroleum spirit elution) gave, after concentration of the relevant fractions (R_f = 0.3), the title compound **11** (1.11 g, 82%), as an amber gum.

$[\alpha]_D$ +128.5 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.08 (d, *J* = 7.6 Hz, 1 H), 7.66 (t, *J* = 7.6 Hz, 1 H), 7.53 (t, *J* = 7.6 Hz, 1 H), 7.29 (d, *J* = 7.6 Hz, 1 H), 6.64 (br s, 1 H), 4.95 (dd, *J* = 5.2, 3.1 Hz, 1 H), 4.79 (m, 1 H), 3.06 (m, 1 H), 2.92 (dd, *J* = 16.9, 3.4 Hz, 1 H), 1.49 (s, 3 H), 1.44 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 192.9, 148.2, 140.9, 138.4, 133.7, 131.4, 130.9, 129.4, 124.3, 109.9, 73.6, 71.4, 39.6, 28.0, 26.4.

IR: 2988, 2932, 1686, 1523, 1349, 1223, 1060 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{15}NO_5Na$: 312.0848; found: 312.0844.

(3a*R*,10a*S*)-2,2-Dimethyl-3a,5,10,10a-tetrahydro-4*H*-[1,3]dioxolo[4,5-*b*]carbazole (12)

A magnetically stirred solution of compound **11** (51 mg, 0.176 mmol, 1.0 equiv) in MeOH (1 mL) was treated with PtO_2 (16 mg, 0.071 mmol, 0.4 equiv) and maintained under an atmosphere of hydrogen (balloon) at ambient temperatures. After 0.5 h, the reaction mixture was filtered through a pad of diatomaceous earth which was then washed with EtOAc (*ca.* 30 mL). The combined filtrates were concentrated under reduced pressure and the resulting brown oil was subjected to flash chromatography (silica, 3:7 v/v EtOAc/petroleum spirit elution). Concentration of the relevant fractions (R_f = 0.4) gave the title indole **12** (37 mg, 87%) as a light-brown oil containing a few small crystals.

$[\alpha]_D$ –13.4 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.88 (br s, 1 H), 7.51 (d, *J* = 7.1 Hz, 1 H), 7.27 (d, *J* = 7.1 Hz, 1 H), 7.14 (m, 2 H), 4.64 (m, 2 H), 3.09 (m, 2 H), 3.00 (m, 2 H), 1.45 (s, 3 H), 1.43 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 136.2, 130.7, 127.2, 121.1, 119.3, 117.7, 110.6, 108.1, 106.5, 73.7, 73.5, 27.7, 27.0, 25.4, 24.6.

IR: 3399, 3340, 2922, 2853, 1455, 1374, 1217, 1057, 743 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* [M–CH_3+MeOH]$^+$ calcd for $C_{15}H_{18}NO_3$: 260.1287; found: 260.1281.

(3a*R*,5a*S*,8a*S*,8b*S*)-8-Acetyl-2,2,7-trimethyl-3a,5a,8a,8b-tetrahydro[1,3]dioxolo[4,5-*e*]benzofuran-5(4*H*)-one (14)

A magnetically stirred solution of iodide **3** (70 mg, 0.24 mmol, 1.0 equiv) and pentane-2,4-dione (37 µL, 0.36 mmol, 1.5 equiv) in toluene (2.0 mL) was treated with Cs_2CO_3 (155 mg, 0.48 mmol, 2.0 equiv) and the resulting mixture was heated at 95 °C for 0.33 h before being cooled and quenched with ammonium chloride (5 mL of a saturated aqueous solution). The separated aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v EtOAc/petroleum spirit elution) to afford, after concentration of the relevant fractions (R_f = 0.3), compound **14** (29 mg, 46%) as a tan, crystalline solid.

Mp 122–123 °C; $[\alpha]_D$ +285.5 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.84 (dd, *J* = 5.4, 3.4 Hz, 1 H), 4.69 (dd, *J* = 11.0, 1.8 Hz, 1 H), 4.51 (m, 1 H), 4.26 (br d, *J* = 11.0 Hz, 1 H), 2.73 (m, 1 H), 2.36 (m, 1 H), 2.36 (s, 3 H), 2.28 (d, *J* = 1.5 Hz, 3 H), 1.34 (s, 3 H), 1.31 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 201.4, 193.1, 168.7, 114.0, 108.9, 82.1, 74.9, 72.0, 46.7, 40.3, 29.6, 26.5, 25.5, 15.5.

IR: 2985, 2925, 1737, 1619, 1383, 1367, 1211, 1045 cm^{-1}.

HRMS (ESI, +ve): *m*/*z* [M + Na+MeOH]$^+$ calcd for $C_{15}H_{22}O_6Na$: 321.1314; found: 321.1303.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1952-4557. Included are an outline of the general synthetic protocols employed in this study, plots derived from the single-crystal X-ray analyses of compound **8**, the *N*-hydroxy derivative of compound **12** and of compound **14** together with copies of the ^{1}H and ^{13}C NMR spectra of compounds **2**–**6**, **8**, **9**, **11**, **12** and **14**.

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