

A Low-Cost and Scalable Synthesis of a Cyclohexanone-Related Bifunctional Building Block

Qinghong Zha,[†] Xiaosheng An,[†] Ze-Jun Xu, Wei-Bo Han, and Yikang Wu*Cite This: *ACS Omega* 2021, 6, 30811–30817

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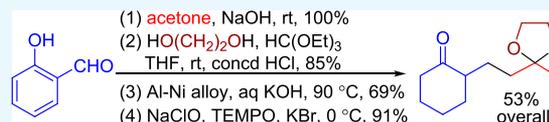


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Supporting Information

ABSTRACT: A practical route to 2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-cyclohexan-1-one was developed, featuring the use of inexpensive starting materials/reagents and readily attainable reaction conditions. The overall transformation was achieved in 53% yield with one chromatographic purification via NaOH-mediated aldol condensation, ethylene glycol protection of the ketone group in the presence of HC(OEt)₃/concd HCl, saturation of the C=C bond and the benzene ring with Al–Ni alloy in aqueous KOH, and oxidation of the intermediate cyclohexanol with aqueous NaClO/TEMPO/KBr.



INTRODUCTION

During our studies on synthesis^{1,2} of organic peroxides/natural products and development of synthetic methodologies, at times, we found ourselves in need of a monosubstituted cyclohexanone, 2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-cyclohexan-1-one (**1**, Figure 1), either as a convenient starting material for constructing various target molecules or as a suitable substrate for testing synthetic methodologies. Through

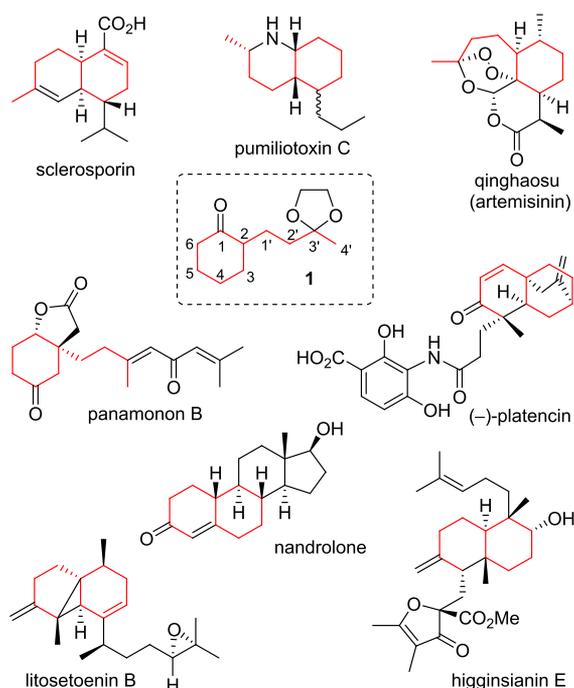


Figure 1. Structures of **1** and a few representatives of a large number of natural products/bioactive compounds that apparently incorporate the carbon framework (red) of ketone **1**.

the repeated accidental demand for **1** in different projects over the years, we gradually come to realize the so far largely unrecognized potential of this small compound as a versatile building block in synthesis in general. Indeed, a great many natural products and bioactive compounds contain a cyclohexane motif and in quite a few cases, it is even possible to identify an intact carbon framework of **1** incorporated in the given target structures as exemplified by sclerosporin,^{3a} pumiliotoxin C (alkaloid cis-195 J),^{3b} qinghaosu,⁴ panamonon B,^{1c} platencin,⁵ nandrolone,⁶ litosetoenin B,^{7a} and higginsianin E^{7b} (Figure 1). Also, ketone **1** indeed allows for many different ways to incorporate itself into various target structures. For example, the methylene groups α to the carbonyl group in **1** can be regioselectively deprotonated under either kinetic⁸ or thermodynamic⁹ control to offer the possibility of reacting at either C-2 or C-6. Alternatively, the enolates may be further converted to the corresponding silyl enol ether and treated with Pd(OAc)₂¹⁰ or IBX¹¹ to install a C=C bond conjugate to the carbonyl group at either C2/C-3 or C-5/C-6 to activate either C-3 or C-5 as desired. Also, in either case, C-4 would be activated as it becomes an allylic position. The silyl enol ethers may be coupled with ring-expansion¹² (mediated by a 3/6 ring fused bicyclic species) to generate the corresponding cycloheptenones. By using Stoltz^{5,13} allylation, even enantioselective installation of a quaternary center at C-2 is possible. In addition, the cyclohexanone ring of **1** may be regioselectively oxidized to furnish the corresponding lactone and/or linear multifunctionalized product(s). Finally, the functionalized sidechain of **1** may also open up many additional options,

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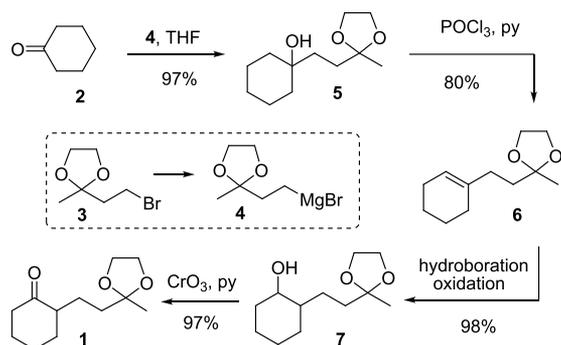
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including annulation to construct a bicyclic system and attachment of other subunits to the desired positions of the chain.

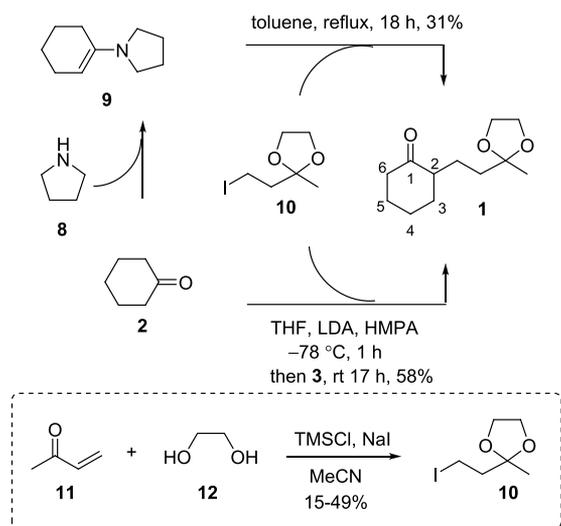
However, despite its unassuming structure, ketone **1** is far not as readily attainable as one would presume, especially when needed in large quantities (e.g., >10 g).¹⁴ The first¹⁵ documented synthesis of **1** appeared in 1976, which was a four-step sequence: (1) the addition of the Grignard reagent **4** to cyclohexanone, (2) dehydration, (3) hydroboration/oxidation,¹⁶ and (4) Collins¹⁷ oxidation (Scheme 1).

Scheme 1. The First Route to Ketone 1 Documented in the Literature



Later, in 1992, Moeller and Tiano¹⁸ reported another route that relied on the alkylation of enamine **9** with iodide **10**¹⁹ (Scheme 2). This approach is simpler than the first one, but

Scheme 2. Two Previous Routes to 1, with the Most Convenient/Practical Entry to the Alkylating Agent 10 Shown at the Bottom (Boxed)



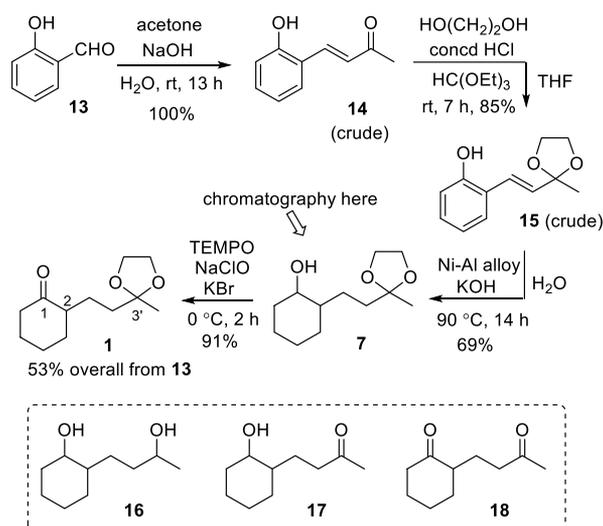
still suffered from serious drawbacks, with the yield for the alkylation step being only 31%.²⁰ In a previous^{1a} work, we attempted direct alkylation of cyclohexanone **2** with iodide **10** and obtained **1** in 58% yield from **2** (or <28%²¹ overall from **11**). However, because of the involvement of LDA (lithium diisopropylamide), HMPA (*N*-hexamethyl phosphoric triamide, a known carcinogen), and strict moisture-free/oxygen-free conditions, that approach also has apparent confines and is thus only suitable for small-scale synthesis. The limitations of the existing methods, together with the hidden problem

common to all iodide **10**-based routes, i.e., the capricious²² (often lower than originally reported) yield of iodide **10**, made it rather difficult to acquire **1** in ample quantities for large-scale and/or multistep syntheses. All these prompted us to seek a more practical route to ketone **1**, which may be readily adapted for multi-ten gram or even larger scales without involving either expensive reagents or moisture-free/oxygen-free conditions.

RESULTS AND DISCUSSION

The eventually developed sequence is shown in Scheme 3. The desired carbon framework was derived from the inexpensive and readily available salicylaldehyde **13** and acetone.

Scheme 3. The Present Route to Ketone 1



The aldol condensation reaction was performed in aqueous NaOH at ambient temperature, affording the known²³ enone-phenol **14**. The side products caused by unavoidable concurrent self-condensation of acetone were effectively removed by extraction of the basic reaction mixture with Et₂O before final acidification with HCl to generate phenol **14** from the corresponding enolate. The crude **14** thus obtained was proven to be pure enough and used as such in the next step of reaction.

Subsequent protection of the ketone group was achieved via reaction with HO(CH₂)₂OH in THF with concd HCl as the catalyst and HC(OEt)₃ as a water scavenger. To remove the undesired non-phenolic side products, the acidic reaction mixture was first basified to pH 13–14 by addition of NaOH and extracted with Et₂O. The strongly basic aqueous phase was then neutralized very carefully with diluted HCl to pH 6 to give crude phenol-ketal **15**,²⁴ which was pure enough for the next step.²⁵

Saturation of the C=C bond and the phenyl ring in **15** was first attempted by hydrogenation over conventionally employed catalysts including Ra–Ni or 10% Pd–C with or without an acetyl protecting group at the phenol OH. However, the yield of the desired cyclohexanol **7** varied drastically from run to run without any obvious causes. Involvement of H₂ in the experiment also imposed additional inconvenience.²⁶ For these reasons, later, we turned our attention to the inexpensive Al–Ni alloy (the starting material for preparation of Raney Nickel), which had been reported to

be effective in the saturation of various phenols in aqueous KOH or NaOH at 90 °C.²⁷ Use of Al–Ni alloy to saturate the C=C bond conjugate to either a phenyl ring or a carbonyl group is also known, though the reactions were performed under slightly different conditions (without added KOH or NaOH).^{28,29}

Gratifyingly, stirring of crude ketal **15** with Ni–Al alloy in aqueous KOH at 90–91 °C for 14 h indeed led to full reduction³⁰ of both the phenyl ring and the C=C bond, giving the expected alcohol **7** as a 1:1 mixture of two diastereomers along with small amounts of side product(s)^{31,32} that were substantially more polar than **7**.

Direct use of the crude **7** in the subsequent oxidation was then examined under the NaClO/TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl)/KBr³³ conditions.³⁴ The reaction proceeded smoothly as expected. However, the product **1** thus obtained was very difficult to purify because of the similar polarity of ketone **1** and the side product (which later was proven to be the known³⁵ dione **18**). In comparison, the polarity difference observed between the components of crude **7** was much larger. Therefore, the chromatographic purification initially planned to be done at the end of the whole synthetic sequence was then performed before the final oxidation.

Removal of the impurity (i.e., diol **16**) from crude **7** indeed solved the problem. Thus, oxidation of the 1:1 mixture of *cis*- and *trans*-**7** afforded clean **1** in 91% yield after removal of the TEMPO-related colored species by filtration through silica gel.³⁶

CONCLUSIONS

We have developed an alternative approach to the synthesis of ketone **1**, featuring the use of inexpensive starting materials/reagents, readily attainable reaction conditions, and rather simple operations. As a consequence, ketone **1** now becomes much easier³⁷ to access than ever before; the main barrier to the broad application of this versatile bifunctional building block in synthesis thus has been removed.

EXPERIMENTAL SECTION

General Remarks. All solvents and reagents were used as received from commercial sources. Column chromatography was performed on silica gel (300–400 mesh) under slightly positive pressure. PE stands for petroleum ether (b.p. 60–90 °C). The Al–Ni alloy had an Al/Ni ratio of 50/50. Melting points were uncorrected (measured on a hot-stage melting point apparatus equipped with a microscope). IR spectra were measured with a Nicolet 380 infrared spectrophotometer. NMR spectra were recorded with an Agilent DD2 500 NMR (operating at 500 MHz for ¹H). HRMS (EI) data for **15** were obtained with a Waters Premier GC-TOF-MS spectrometer. HRMS (FI) data for **7** were obtained with a JEOL-AccuTOF-GCv4G-GCT MS spectrometer.

(E)-4-(2-Hydroxyphenyl)but-3-en-2-one (14). To a solution of salicylic aldehyde (20.00 g, 163.77 mmol) in acetone (118 mL) stirred at ambient temperature was added a freshly prepared aq. NaOH (2.0 M, 98 mL, ca. 196 mmol). The colorless solution of salicylic aldehyde first turned yellow, then burgundy, and finally dark-red. The turbid mixture was stirred at ambient temperature for 13 h (TLC on silica gel plate, developed with 3:1 PE/EtOAc, showed full consumption of **13**). Acetone was removed by rotary evaporation under an

aspirator vacuum. Water (100 mL) was added to the dark-red residue (containing some precipitates), followed by Et₂O (100 mL). The mixture was stirred at ambient temperature for ca. 20 min before being transferred to a separatory funnel. The dark-red aqueous layer was drained, and the yellow upper (ethereal) layer was washed with small portions of 2.0 M NaOH and H₂O (until TLC showed no more **14** in the ethereal phase). The combined aqueous layers (in a beaker) were carefully acidified with 2% HCl (ca. 160 mL). Some yellow solids formed during the acidification. To the mixture was added EtOAc (400 mL). The two-phase mixture was transferred to a separatory funnel. The lower (aqueous) layer (ca. pH 5) was drained. The yellow organic layer in the funnel was washed with brine (30 mL) and dried over anhydrous Na₂SO₄. Removal of the drying agent by filtration and the solvent by rotary evaporation left crude **14** as a yellow solid (26.66 g, 164 mmol, 100% from **13**), which was pure enough and used as such in the next step. For comparison, the following data were also collected on crude **14**: m.p. 139–142 °C. ¹H NMR (500 MHz, CDCl₃) δ 7.86 (d, *J* = 16.4 Hz, 1H), 7.52–7.47 (a lump, 0.4H, OH), 7.47 (br dd, *J* = 7.6, 1.2 Hz, 1H), 7.263 (br s, 0.6H, OH), 7.260 (br dt, *J* = 1.5, 7.5, 1H), 7.05 (br d, *J* = 16.4 Hz, 1H), 6.93 (br d, *J* = 7.5 Hz, 1H), 6.92 (br t, *J* = 7.5 Hz, 1H), 2.43 (s, 3H); ¹³C{¹H} NMR (125 MHz, CDCl₃) δ 201.4, 156.2, 141.0, 132.1, 129.9, 127.9, 121.6, 120.8, 116.7, 27.0. FT-IR (KBr) 3355, 3065, 3023, 1673, 1641, 1618, 1603, 1499, 1462, 1420, 1356, 1326, 1305, 1253, 1223, 1191, 1159, 1092, 1042, 1008, 972, 862, 795, 761 cm⁻¹.

(E)-2-(2-(2-Methyl-1,3-dioxolan-2-yl)vinyl)phenol (15). To a yellow solution of the above-obtained crude enone **14** (22.11 g, 136 mmol) in THF (220 mL) stirred at ambient temperature were added HO(CH₂)₂OH (76 mL, 1.36 mol), HC(OEt)₃ (45 mL, 272 mmol), and concd HCl (36%, 0.14 mL). The dark-red mixture was stirred at ambient temperature for 7 h (TLC showed completion of the reaction after stirring for 5 h). Freshly prepared aq. NaOH (2.0 M, 40 mL) was carefully added. Most of the organic volatiles in the mixture were removed by rotary evaporation under aspirator vacuum. To the residue was added H₂O (20 mL) followed by Et₂O (100 mL). The two-phase mixture was stirred at ambient temperature for 15 min before being transferred to a separatory funnel. The dark-red lower (aqueous) layer was drained. The upper yellow ethereal layer was washed with small portions of 2.0 M NaOH and H₂O until TLC showed the absence of **15** in the ethereal phase. The combined aqueous layers were acidified very carefully with 2% HCl to pH 7 (further acidification would lead to significant hydrolysis of the ketal). The red-brown mixture was transferred to a separatory funnel. EtOAc (400 mL) was added. Small portions of 2% HCl were then introduced slowly with the funnel shaken after each addition until two yellow clear phases clearly formed on standing. The lower (aqueous) layer was drained (ca. pH 6) and extracted with EtOAc (300 mL). The combined organic layers were washed with water (40 mL × 3) and brine (30 mL × 3) and dried over anhydrous Na₂SO₄. Removal of the drying agent by filtration and the solvent by rotary evaporation left crude **15** as a yellow solid (23.97 g, 116 mmol, 85% from **14**, m.p. 116–121 °C with the ¹H and ¹³C{¹H} NMR spectra for this crude sample shown in the Supporting Information for comparison), which was used as such in the next step.

A small portion of the above crude **15** was purified by column chromatography (6:1 PE/EtOAc) on silica gel to give the following data for pure **15**: m.p. 118–120 °C. ¹H NMR

(500 MHz, CDCl_3) δ 7.37 (br dd, $J = 7.8, 1.4$ Hz, 1H), 7.13 (br dt, $J = 7.8, 1.6$ Hz, 1H), 6.96 (br d, $J = 16.1$ Hz, 1H), 6.90 (br dt, $J = 7.3$ Hz, 1H), 6.78 (br d, $J = 8.0$ Hz, 1H), 6.23 (d, $J = 16.1$ Hz, 1H), 5.54–5.50 (a lump, 1H, OH), 4.06–3.96 (m, 4H), 1.59 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 153.5, 131.1, 129.1, 128.0, 124.6, 123.4, 121.0, 116.1, 108.1, 64.7, 25.4. FT-IR (KBr) 3356, 2985, 2894, 1644, 1619, 1601, 1499, 1454, 1371, 1357, 1043, 1266, 1181, 1159, 1089, 1040, 989, 955, 940, 851, 816, 761 cm^{-1} . MS (EI) m/z (%): 206 (M^+ , 16), 191 ($\text{M}^+ - \text{CH}_3$, 100), 145 (45), 131 (10), 115 (13), 103 (29); HRMS (EI positive) m/z : M^+ calcd for $\text{C}_{12}\text{H}_{14}\text{O}_3$ 206.0937, found 206.0941.

(1*R,2*R**)-2-(2-(2-Methyl-1,3-dioxolan-2-yl)ethyl)cyclohexan-1-ol (cis-7) and (1*S**,2*R**)-2-(2-(2-Methyl-1,3-dioxolan-2-yl)ethyl)cyclohexan-1-ol (trans-7).** A solution of KOH (6.38 g, 113.7 mmol) in H_2O (425 mL) was added to a 1 L three-necked flask equipped with a mechanical stirrer³⁸ and a condenser. The above-obtained crude **15** (19.54 g, 94.74 mmol) was then introduced with stirring at ambient temperature through the side neck. The mixture turned dark-red soon (still with some undissolved solids). Stirring was continued at ambient temperature for 20 min. Al–Ni alloy (58.62 g) was added in small portions over ca. 10 min. Stirring was continued at ambient temperature for another 30 min and then in an oil bath (103 °C). The temperature of the reaction mixture gradually reached 90–91 °C and remained stable throughout the whole reaction time. The dark-red mixture gradually turned first yellow, then gray, and finally milky (with some dark solids precipitated at the bottom). After heating/stirring for 4 h, a yellow oily layer gradually formed and floated on the aqueous mixture. Another portion of Al–Ni (19.0 g) was then added in small portions. Stirring was continued at the same temperature for 5.5 h before an additional portion of Al–Ni alloy (5.0 g) was added carefully. Stirring/heating was then continued for another 4 h, when TLC (2:1 PE/EtOAc) showed completion of the reaction. The oil bath was removed. After the mixture was cooled to ambient temperature, EtOAc (100 mL) was added. The mixture was stirred for 10 min and then allowed to stand still overnight. Most of the yellow oily upper layer (crude **7**) was transferred to a beaker using a pipette. The mixture was then filtered through Celite. The filter cake was washed in turn with H_2O (200 mL \times 3) and EtOAc (200 mL \times 3). The combined biphasic filtrate/washings were transferred to a separatory funnel. The phases were separated. The aqueous layer was extracted with EtOAc (200 mL \times 2). The combined organic layers (including the initial yellow oil taken out before filtration) were washed with brine (60 mL) and dried over anhydrous Na_2SO_4 . Removal of the drying agent and the solvent left a yellowish oil (19.02 g), containing mostly **7** and small amounts of diol **16** as well as traces of other unidentified side-products.

A major portion of the above-obtained yellowish oil (16.07 g) was purified by column chromatography on silica gel (4:1 PE/EtOAc) to give a ca. 1:1 mixture of *cis*-**7** and *trans*-**7** as a yellowish oil (11.89 g, 55.48 mmol, 69.3% from **15**, with the ^1H and ^{13}C NMR shown in the Supporting Information), along with (eluting with 1:1 PE/EtOAc) diol **16** (3.073 g, 17.8 mmol, 22.2% from **15**) as a yellowish oil.

A very small portion of the above-obtained crude yellowish oil (after removal of the solvent, before column chromatography) was subjected to preparative TLC (developing with 2:1 PE/EtOAc) to give samples of *cis*-**7** and *trans*-**7**, from which the following spectroscopic data were collected. Data for *cis*-**7**

(the less polar isomer, a colorless oil): ^1H NMR (500 MHz, CDCl_3) δ 3.96–3.89 (m, 4H), 3.88–3.85 (unresolved m, 1H), 2.00–1.81 (a lump, 1H, OH), 1.81–1.74 (m, 1H), 1.70–1.60 (m, 3H), 1.59–1.50 (m, 1H), 1.48–1.37 (m, 4H), 1.37–1.30 (m, 3H), 1.30 (s, 3H), 1.27–1.16 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 110.4, 69.0, 64.7, 41.6, 36.5, 33.1, 26.9, 26.1, 25.3, 23.9, 20.6. FT-IR (film of a concd solution in CH_2Cl_2) 3462, 2981, 2930, 2862, 1447, 1377, 1317, 1253, 1222, 1157, 1135, 1109, 1077, 1046, 975, 948, 859 cm^{-1} . HRMS (FI positive) m/z : M^+ calcd for $\text{C}_{12}\text{H}_{22}\text{O}_3$ 214.1563, found 2014.1567. Data for *trans*-**17** (the more polar isomer, a colorless oil): ^1H NMR (500 MHz, CDCl_3) δ 3.97–3.90 (m, 4H), 3.22 (dt, $J = 4.5, 9.5$ Hz, 1H), 1.97–1.91 (m, 1H), 1.86–1.69 (m, 5H), 1.66–1.55 (m, 2H), 1.31 (s, 3H), 1.29–1.10 (m, 5H), 0.92 (br dq, $J = 3.8, 12.9$ Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 110.5, 74.6, 64.8, 64.7, 45.3, 36.0, 35.7, 30.4, 26.4, 25.7, 25.1, 23.9. FT-IR (film of a concd solution in CH_2Cl_2) 3440, 2981, 2927, 2857, 1449, 1377, 1343, 1296, 1255, 1221, 1158, 1103, 1050, 947, 912, 861 cm^{-1} . HRMS (FI positive) m/z : M^+ calcd for $\text{C}_{12}\text{H}_{22}\text{O}_3$ 214.1563, found 2014.1562.

2-(2-(2-Methyl-1,3-dioxolan-2-yl)ethyl)cyclohexan-1-one (1). A commercially available aqueous NaClO ³⁹ solution (containing >5.2% of active chlorine, with free base 7–8%, 100 mL) was diluted with distilled H_2O (100 mL). To the resulting solution was added powdered NaHCO_3 (36.00 g, 428 mmol). The mixture was stirred at ambient temperature until most NaHCO_3 was dissolved. The mixture was then allowed to stand, and the yellowish supernatant (ca. 200 mL, pH 9–10)⁴⁰ was ready to use in the following oxidation.

TEMPO (401 mg, 2.57 mmol) was added to a solution of alcohol **7** (the above-obtained 1:1 mixture of *cis* and *trans* isomers, 11.00 g, 51.33 mmol) in CH_2Cl_2 (103 mL) stirred in an ice-water bath (giving a light orange solution) followed by a solution of KBr (611 mg, 5.13 mmol) in distilled H_2O (10 mL). The above-obtained supernatant of NaClO (pH 9–10, estimated to be 0.4 M in NaClO , ca. 200 mL) was then introduced slowly. The addition first resulted in a dark-brown color, which faded gradually to orange. After completion of the addition of NaClO , stirring was continued in the ice-water bath for another 2 h, when TLC (2:1 PE/EtOAc) showed full consumption of the starting alcohol **7**. To the yellow mixture was added Et_2O (30 mL) followed by H_2O (15 mL). The phases were separated. The aqueous layer was back-extracted with Et_2O (200 mL \times 2). The combined organic layers were washed with saturated aqueous Na_2SO_3 (50 mL \times 2) and brine (50 mL) and dried over anhydrous Na_2SO_4 . Removal of the drying agent and the solvent left a light-brown/gray crude oil (11.91 g, 52.71 mmol, 103% yield from **7**), which was filtered through a short column of silica gel (ϕ 8 \times 10 cm, rinsing with 2–3 L of 7:1 PE/EtOAc) to remove the colored TEMPO-related species (remained on top of the silica gel column). The combined filtrate/washings were rotary evaporated to give the known **1** as a yellowish oil (9.907 g, 46.67 mmol, 91% from **7**).

Data for **1**: ^1H NMR (500 MHz, CDCl_3 , assigned with the aid of COSY and HSQC) δ 3.96–3.89 (m, 4H, H-ketal), 2.38 (br dtd, $J = 13.4, 4.1, 1.1$ Hz, 1H, H-6 equatorial), 2.281 (br ddd, $J = 13.4, 11.3, 4.1$ Hz, 1H, H-6 axial), 2.280 (br dtd, $J = 12.5, 6.8, 6.4$ Hz, 1H, H-2), 2.10 (br double multiplet with the J for the doublet = 14.1 Hz, 1H, H-3 equatorial), 2.02 (br double multiplet with the J for the doublet = 14.1 Hz, 1H, H-5 equatorial), 1.89 (ddd, $J = 13.4, 6.5, 5.2$ Hz, 1H, H-2'), 1.88–1.82 (m, 1H, H-1'), 1.68–1.63 (m, 1H, H-5 axial), 1.69–1.61

(m, 1H, H-4 equatorial), 1.64–1.59 (m, 1H, H-1'), 1.61 (partially resolved dtd, $J = 13.5, 11.5, 5.0$ Hz, 1H, H-4 axial), 1.39 (br dq, $J = 11.0, 4.1$ Hz, 1H, H-3 axial), 1.32 (s, 3H, H-4'), 1.29 (partially resolved ddd, $J = 13.5, 11.5, 6.2$ Hz, 1H, H-2'); $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3 , assigned with the aid of DEPT, COSY, and HSQC) δ 213.2, 110.2, 64.8, 50.8, 42.2, 36.6, 34.2, 28.2, 25.0, 24.1, 23.9.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.1c05159>.

^1H and ^{13}C NMR spectra of all compounds and DEPT, COSY, HSQC, HMBC of **1**, IR and HRMS of *cis*-**7**, *trans*-**7**, and **15** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Yikang Wu – State Key Laboratory of Bioorganic and Natural Products Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China; orcid.org/0000-0003-4501-5401; Email: yikangwu@sioc.ac.cn

Authors

Qinghong Zha – State Key Laboratory of Bioorganic and Natural Products Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Xiaosheng An – State Key Laboratory of Bioorganic and Natural Products Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Ze-Jun Xu – State Key Laboratory of Bioorganic and Natural Products Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Wei-Bo Han – State Key Laboratory of Bioorganic and Natural Products Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Complete contact information is available at:

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Author Contributions

[†]Q.Z. and X.A. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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(20) The corresponding overall yield of **1** from the starting material of iodide **10** would be much lower. For instance, the overall yield from **11** would be only 5–15%.

(21) With the corresponding overall yield of **1** from **11** being 9–28%.

(22) Presumably is caused by the great tendency of methyl vinyl ketone (MVK) to polymerize. Another problem associated with MVK is the accessibility: In China, MVK is a strictly regulated substance, which is practically impossible to purchase and definitely not permitted to store in ordinary laboratories.

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J. Org. Chem. **2008**, 2759–2766 (compound **7** therein, 58% yield, m.p. 139–140 °C).

(24) Further acidification led to hydrolysis of substantial amounts of **15** back to **14**.

(25) As compound **15** has never been reported before, for complete documentation, its physical and spectroscopic data are also collected on a small purified sample.

(26) For safety reasons, in our institute, performing hydrogenation in ordinary laboratories is prohibited; such experiments must be carried out in a special laboratory shared by the whole institute, and booking a space there prior to every use is required.

(27) (a) Tsukinoki, T.; Kanda, T.; Liu, G.-B.; Tsuzuki, H.; Tashiro, M. Organic reaction in water. Part 3: A facile method for reduction of aromatic rings using a Raney Ni-Al alloy in dilute aqueous alkaline solution under mild conditions. *Tetrahedron Lett.* **2000**, *41*, 5865–5868 (the original report). (b) Tan, S.-L.; Liu, G.-B.; Gao, X.; Thiemann, T. Raney Ni-Al alloy-mediated reduction of alkylated phenols in water. *J. Chem. Res.* **2009**, 5–7.

(28) (a) Rayhan, U.; Kowser, Z.; Islam, M. N.; Redshaw, C.; Yamato, T. Reduction of phenylacetylenes using Raney Ni-Al alloy, Al powder in the presence of noble metal catalysts in water. *ARKIVOC* **2018**, 241–251 (in the presence of Al powder and Pt/C in sealed tubes). (b) Simion, C.; Mitona, Y.; Katayama, Y.; Simion, A. M. Reduction of α,β -unsaturated carbonyl compounds and 1,3-diketones in aqueous media, using a Raney Ni-Al alloy. *Rev. Roum. Chim.* **2020**, *65*, 51–55 (benzene rings were not saturated).

(29) For related reduction of simple aromatics using Al-Ni alloy in neutral water in the presence of Al powder and co-catalysts, cf: (a) Rayhan, U.; Kwon, H.; Yamato, T. Reduction of aromatic compounds with Al powder using noble metal catalysts in water under mild reaction conditions. *C. R. Chim.* **2014**, *17*, 952–957. (b) Rayhan, U.; Do, J.-H.; Arimura, T.; Yamato, T. Reduction of carbonyl compounds by Raney Ni-Al alloy and Al powder in the presence of noble metal catalysts in water. *C. R. Chim.* **2015**, *18*, 685–692.

(30) There have been a large number of reports on the Al-Ni alloy based reduction of phenyl rings in water, but to date, almost all the studies are methodological rather than synthetic in nature, involving only simple monofunctional substrates. Perhaps this is why such a nice inexpensive/practical reduction method appears to be largely overlooked by the synthetic community.

(31) Oxidation of a mixture of these side products (free from any methyl ketone **17** as shown by the ¹H NMR) with NaClO/TEMPO/KBr gave the known dione **18** in 72% yield as the only observed product, indicating that the starting material must consist mainly of the diastereomers of diol **16**. Note that before the C-3' must have been reduced by Al-Ni alloy/aq. KOH at 90 °C, the ketal function was hydrolyzed to a free ketone under strongly basic conditions, an event somewhat unexpected and thus worthy of mentioning.

(32) For Al-Ni alloy reduction of simple ketones, see: (a) Tomin, A.; Lazarev, A.; Bere, M. P.; Redjeb, H.; Török, B. Selective reduction of ketones using water as a hydrogen source under high hydrostatic pressure. *Org. Biomol. Chem.* **2012**, *10*, 7321–7326. (b) Suceveanu, M.; Raicopol, M.; Enache, R.; Finaru, A.; Roşca, S. I. Selective reductions of the carbonyl compounds and aryl halides with Ni-Al alloy in aqueous alkali medium. *Lett. Org. Chem.* **2011**, *8*, 690–695.

(33) Anelli, P. L.; Carlo Biffi, C.; Montanari, F.; Quici, S. Fast and Selective Oxidation of Primary Alcohols to Aldehydes or to Carboxylic Acids and of Secondary Alcohols to Ketones Mediated by Oxoammonium Salts under Two-Phase Conditions. *J. Org. Chem.* **1987**, *52*, 2559–2562.

(34) For another scalable oxidation protocol (with CH₂Cl₂ as the solvent), which gave **1** in 82% yield, see: Taber, D. F.; Amedio, J. C., Jr.; Jung, K.-Y. P₂O₅/DMSO/Triethylamine (PDT): A Convenient Procedure for Oxidation of Alcohols to Ketones and Aldehydes. *J. Org. Chem.* **1987**, *52*, 5621–5622.

(35) Li, N.; Zhang, X.; Xu, X.; Chen, Y.; Qiu, R.; Chen, J.; Wang, X.; Yin, S.-F. Synthesis and Structures of Air-Stable Binuclear Hafnocene Perfluorobutanesulfonate and Perfluorobenzenesulfonate and their Catalytic Application in C-C Bond-Forming Reactions. *Adv. Synth.*

Catal. **2013**, *355*, 2430–2440 (compound **9b** therein, with NMR data and spectra shown on pages S11 and S48, respectively, of the [Supporting Information](#) of that article).

(36) The crude product was rather pure, with ^1H and ^{13}C NMR essentially the same as those recorded after removal of the colored species by filtration through silica gel.

(37) Without this route, it would have been impossible for us to get enough quantity of ketone **1** for the total synthesis of panamonon B (ref 1c).

(38) It is possible to use a magnetic stirrer in sub-gram-scale experiments, though some of the Al–Ni and the Ra–Ni formed during the reaction might stick to the stirring bar. However, for larger-scale experiments, a mechanical stirrer proved necessary for effective suspension of the solids in the reaction mixture.

(39) CAS [7681-52-9].

(40) It was not possible to use pH test paper here because of the bleaching effect of NaClO; a pH-meter was used.