

Safe Execution of a Large-Scale Ozonolysis: Preparation of the Bisulfite Adduct of 2-Hydroxyindan-2-carboxaldehyde and Its Utility in a Reductive Amination

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Abstract:

Several routes to bisulfite adduct **2** were explored, the most efficient of which involved vinyl Grignard addition to 2-indanone followed by ozonolysis and workup with aqueous NaHSO₃ to effect reduction and bisulfite formation in a single pot. The safety and calorimetry of this ozonolysis reaction was studied, and the safe scale-up to 3 kg of olefin is described. The utility of bisulfite adduct **2** as an aldehyde surrogate in a reductive amination reaction is also described.

Introduction

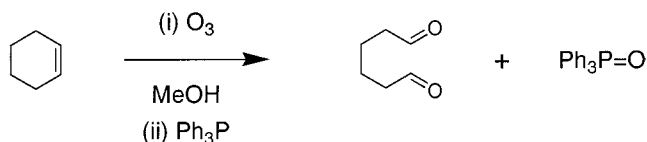
Ozonolysis of olefins is a well-precedented method for preparation of ketones and aldehydes.² From an atom economy perspective, few reactions surpass the efficiency of this procedure. For example, in the ozonolysis of cyclohexene to 1,6-hexanedial (Scheme 1),³ two of the three oxygen atoms in ozone are transferred to the product, with the third oxygen captured by a suitable reducing agent in the workup (e.g., Ph₃P to Ph₃PO).

We recently had need for effecting a reductive amination with aldehyde **1**. We found that isolation of this aldehyde as its bisulfite adduct **2** (Scheme 2) offered significant advantages in terms of handling ease and stability (e.g., aldehyde **1** readily forms dimers and higher oligomers). This contribution describes an efficient preparation of bisulfite adduct **2**, the safety assessment and calorimetry work done to support a large-scale ozonolysis, and the utility of **2** in a representative reductive amination.

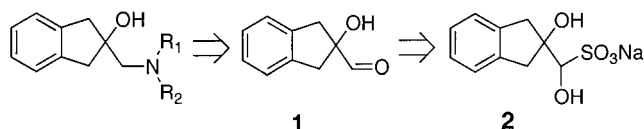
Discussion

1. Preparation of Bisulfite Adduct 2. Our first synthesis of aldehyde **1** is shown in Scheme 3, and utilizes a vinylmetal species as an acyl anion equivalent, a well-precedented strategy.⁴ Vinyl Grignard addition to 2-indanone using commercial CH₂=CHMgBr in tetrahydrofuran (THF) pro-

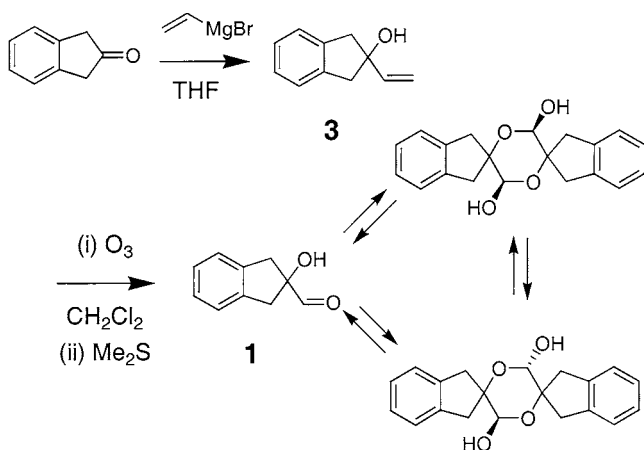
Scheme 1



Scheme 2



Scheme 3



vided ca. 40% conversion to the tertiary allylic alcohol **3**⁵ due to competitive enolization of the starting ketone. The alcohol could be purified by chromatography, or more conveniently, by extraction of the starting ketone with aqueous NaHSO₃ (presumably via formation of the water-soluble bisulfite adduct). Ozonolysis of the terminal olefin in CH₂Cl₂ at -78 °C followed by reductive workup with Me₂S provided a complex mixture of products by ¹H NMR, in which free aldehyde **1** was a minor component. However,

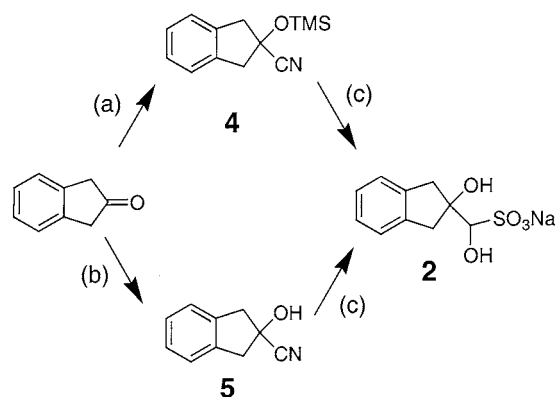
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(2) (a) Lee, D. G.; Chen, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 7, pp 541–591. (b) Criegee, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 745. (c) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1978; Vol. 1.

(3) Knowles, W. S.; Thompson, Q. E. *J. Org. Chem.* **1960**, *25*, 1031.

(4) (a) Gillespie, D. T. C.; Jefferies, P. R.; Macbeth, A. K.; Thompson, M. J. *J. Chem. Soc.* **1955**, 665. (b) Barrett, A. G. M.; Graboski, G. G.; Sabat, M.; Taylor, S. J. *J. Org. Chem.* **1987**, *52*, 4693. (c) Carreira, E. M.; Du Bois, J. J. *Am. Chem. Soc.* **1995**, *117*, 8106. (d) Caron, S.; Stoermer, D.; Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9126.

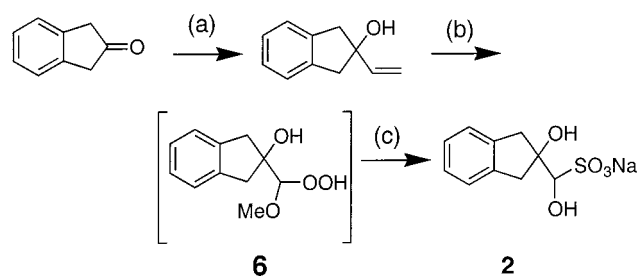
(5) This alcohol has also been prepared by the treatment of 2-indanone with 2 equiv of the ylide derived from trimethylsulfonium bromide and base, which proceeds via the corresponding epoxide: Harnett, J. J.; Alcaraz, L.; Mioskowski, C.; Martel, J. P.; Gall, T. L.; Shin, D.-S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 2009.

Scheme 4^a

^a Conditions: (a) ZnI₂, TMSCN, 18-crown-6. (b) KCN, Na₂S₂O₅, aq MTBE. (c) DIBAL, PhCH₃; NaHSO₃, aq EtOH.

this mixture could be used in a reductive amination and functioned as if free aldehyde were present (or generated in situ). We interpret this result to indicate that the nonenolizable α -hydroxyaldehyde forms a mixture of dimers and higher oligomers which is capable of condensing with the secondary amine to generate the requisite iminium species for successful reductive amination.⁶ Although suitable for laboratory-scale runs, scale-up to multikilogram quantities was likely to be complicated by this poorly characterized mixture of aldehyde oligomers, and a stable, isolable intermediate was sought.

Due to the instability and noncrystallinity of aldehyde **1**, bisulfite adduct **2** was viewed as an attractive intermediate; its first preparation is shown in Scheme 4. Bisulfite adducts of aldehydes are well-precedented, and there are several examples of bisulfite adducts of α -hydroxyaldehydes in the literature,⁷ particularly in the arena of carbohydrate chemistry.⁸ Our first approach to **2** utilized two cyanohydrin approaches, either via cyanohydrin **5**, or the related TMS-cyanohydrin **4** (Scheme 4). Reduction with DIBAL followed by imine hydrolysis generated **2** in modest mass balance (40–50%). The purity of **2** as assayed by ¹H NMR appeared to be quite good, but elemental analysis indicated significant levels of inorganic impurities (e.g., measured carbon levels of <20%, whereas theory for C₁₀H₁₁SO₅Na requires 45.1%). More encouragingly, we were pleased to find that **2** was an easily handled solid and could be purified by trituration or recrystallization from water to provide analytically pure material.

Scheme 5^a

^a Conditions: (a) CH₂=CHMgBr, PhCH₃. (b) O₃, MeOH, -60 °C. (c) aq NaHSO₃, MeOH.

A more efficient synthesis of **2** was realized through an ozonolysis sequence (Scheme 5), similar to that used in the initial preparation of aldehyde **1** (Scheme 3). As described above, competitive enolization of 2-indanone was problematic in the vinyl Grignard addition in THF. We found that displacing the THF in commercial vinyl Grignard with toluene led to significantly reduced enolization. Conversions >95% were realized, and the crude alcohol product was deemed of sufficient purity to take on without further purification. Our rationale for this result is the differing coordination potency of THF versus toluene; in THF the magnesium is solvated more effectively than in toluene and is thus less able to coordinate to the carbonyl oxygen of the substrate. Coordination to the carbonyl oxygen promotes addition over enolization, thus favoring formation of the addition product in the less solvating toluene.

Ozonolysis was effected in MeOH, to trap the carbonyl oxide as the methoxyhydroperoxide (**6**).^{2b,9} This solvent was also preferred over chlorinated solvents from a scale-up and handling perspective. Reduction of the hydroperoxide could be effected by treatment with Me₂S or KI, or most conveniently, with aqueous NaHSO₃.¹⁰ Thus, addition of the MeOH reaction mixture to an aqueous slurry of NaHSO₃ led to reduction of the hydroperoxide (a modest exotherm was noted here, which was controlled by inverse addition, i.e., adding the homogeneous reaction mixture to the aqueous bisulfite slurry). The resulting slurry was then warmed to 60 °C to effect bisulfite formation. Compound **2** was isolated by filtration in 61% overall yield from 2-indanone. Combustion analysis indicated a purity of 56% for this material, which could be recrystallized from 10 vols of water to provide analytically pure material in 47% recovery; the overall yield for analytically pure **2** from 2-indanone was thus 29%. Alternatively, this material could be used directly in the reductive amination (Scheme 6), adjusting the stoichiometry to reflect the measured potency of 56%.

2. Analysis of Potential Thermochemical and Flammability Issues for a Large-Scale Ozonolysis. As the ozonolysis equipment in our scale-up facility had not yet been commissioned at the time of this project, several experiments and decisions were required prior to scale-up. The reaction was first analyzed in an RC-1 calorimeter,

(6) Interestingly, in ref 4a, 1-hydroxy-4-isopropylcyclohexancarboxaldehyde is prepared via ozonolysis of the corresponding vinyl alcohol. Following purification via the bisulfite adduct, isolated aldehyde shows a wide range of melting points (70 to 150 °C), but all samples had the anticipated elemental analysis for the parent aldehyde. ¹H NMR data is not reported, but this is consistent with our observations; an analogous mixture of free aldehyde, dimers, and higher oligomers could account for the variations in melting point.

(7) (a) Tiffany, G. D.; Wright, J. B.; Moffett, R. B.; Heinzelman, R. V.; Strube, R. E.; Aspergren, B. D.; Lincoln, E. H.; White, J. L. *J. Am. Chem. Soc.* **1957**, *79*, 1682. (b) Taub, D.; Pettebone, R. H.; Wendler, N. L.; Tishler, M. *J. Am. Chem. Soc.* **1954**, *76*, 4094.

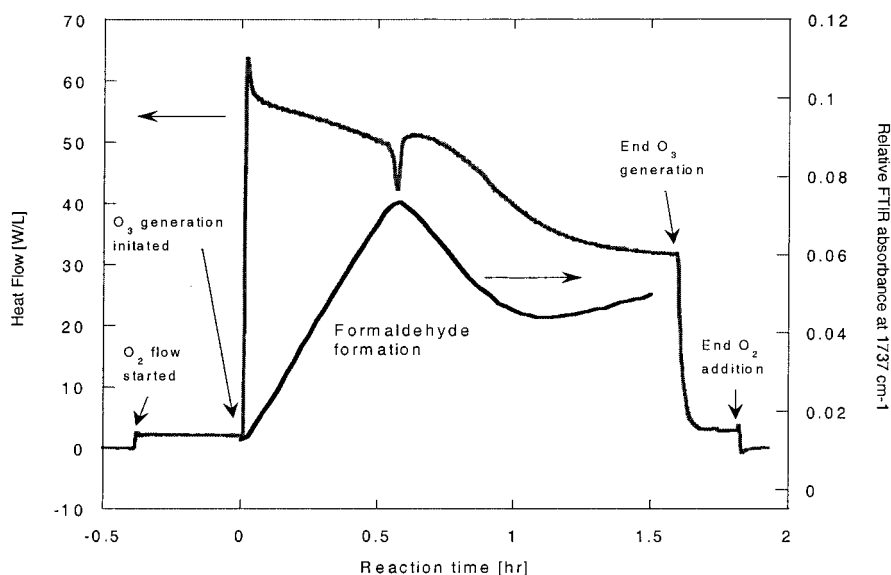
(8) (a) Ingles, D. L. *Aust. J. Chem.* **1959**, *12*, 97. (b) Ingles, D. L. *Aust. J. Chem.* **1966**, *19*, 667. (c) Inouye, S.; Tsuruoka, T.; Ito, T.; Niida, T. *Tetrahedron* **1968**, *24*, 2125. (d) Asahara, K.; Yamade, H.; Yoshida, S. *Chem. Pharm. Bull.* **1991**, *39*, 2662. (e) Dhavale, D. D.; Desai, V. N.; Sindkhedkar, M. D.; Mali, R. S.; Castellari, C.; Trombini, C. *Tetrahedron: Asymmetry* **1997**, *8*, 1475.

(9) (a) Criegee, R.; Schroeder, G. *Chem. Ber.* **1960**, *93*, 689. (b) Thompson, Q. E. *J. Org. Chem.* **1962**, *27*, 4498. (c) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867.

(10) Aqueous sodium sulfite (Na₂SO₃) has been utilized for reduction of ozonides: Callaghan, R. H.; Wilt, M. H. *J. Org. Chem.* **1961**, *26*, 4912.

Table 1. Comparison of three gas input options for the ozonolysis reaction

	option 1: O ₂ feed, no inertion in headspace	option 2: O ₂ feed with N ₂ inertion in headspace	option 3: air feed with N ₂ inertion in headspace
ozone production	6 wt % (5 mol/h)	6 wt % (5 mol/h)	3 wt % (2.5 mol/h)
max. gas flow rate (L/min)	48	48	52
N ₂ inertion flow rate (to achieve 95% N ₂ headspace)	N/A	19× inlet flow	3× inlet flow
basis of safety	solvent vapor concentration should be below lower flammability limit (LFL) at -78 °C, flash point (FP) and LFL were not affected by oxygen content	inert atmosphere, %(O ₂ + O ₃) below MOC; vapor concentration below LFL (although solvent-specific, i.e., MeOH)	inert atmosphere, %(O ₂ + O ₃) below MOC; vapor concentration below LFL
safety/other concerns	minimum ignition energy (MIE) is substantially lower in oxygen atmosphere, entrainment of solvent vapors could form flammable mixture (i.e., below FP)	very high gas flow in vent required to reduce oxygen concentration below 5 vol %	longer reaction times
advantages	high ozone production rate	high ozone production, use of pure MeOH as solvent, ease of workup	allows use of pure methanol as reaction solvent, ease of workup

**Figure 1. Heat flow and relative FTIR absorbance at 1737 cm⁻¹ versus reaction time. The peak at 1737 cm⁻¹ corresponds to the formation of formaldehyde byproduct.**

which showed a $\Delta H_{\text{obs}}^{11}$ of -535 kJ/mol, corresponding to an adiabatic temperature rise of 170 °C (in 10 vols of MeOH). The reaction rate was dose-controlled, which means that if the reactor temperature began to rise the ozone feed could be stopped to eliminate heat generation (this was also observed for the ozonolysis of phenanthrene).¹² Differential scanning calorimetry (DSC) analysis of the reaction mixture showed a moderate exothermic event occurring near 45 °C, liberating 404 J/g of energy. This provided a window greater than 100 °C for a -65 °C reaction temperature and was deemed acceptable for the planned 0 °C quench. The NaHSO₃ quench is also exothermic, with a ΔH_{obs} of <131 kJ/mol, and adiabatic temperature rise of 69 °C. Given the thermal stability results of the reaction solution and the dose-rate control, there was confidence that this reaction could

be performed safely on scale. The graph in Figure 1 shows the heat flow and formation of formaldehyde byproduct as monitored by RC-1 and ReactIR 4000 (Mettler-Toledo) with a DiComp probe versus time. Coincidentally, the completion of the formation of formaldehyde, as noted by the maximum in the IR profile, corresponded to a discontinuity in the heat flow at 0.5 h.

The other primary issue with safe scale-up of this reaction dealt with solvent flammability. There was also concern that the gases present in the headspace had the possibility of forming an explosive mixture of O₂, O₃, and MeOH. To address this issue, we considered dilution with a higher flow rate of an inert gas (N₂). Table 1 shows the analysis of three potential scenarios. Of these, option 3 was chosen as the safest to execute on scale, as it represents a dual basis of safety: both fuel (MeOH) and oxygen/ozone would be kept below the lower flammability limit (LFL) and minimum oxygen concentration (MOC), respectively. The MOC for methanol vapor is 10% v/v O₂ in air,¹³ and the LFL for

(11) This value corresponds to an overall heat flow including heat of reaction, heat of oxygen delivery, and heat of ozone addition and relates to the total heat that would need to be removed by the reactor jacket.

(12) Bailey, P. S.; Erickson, R. E. In *Organic Syntheses*; John Wiley & Sons: New York, 1973; Collect. Vol. V, pp 489–493.

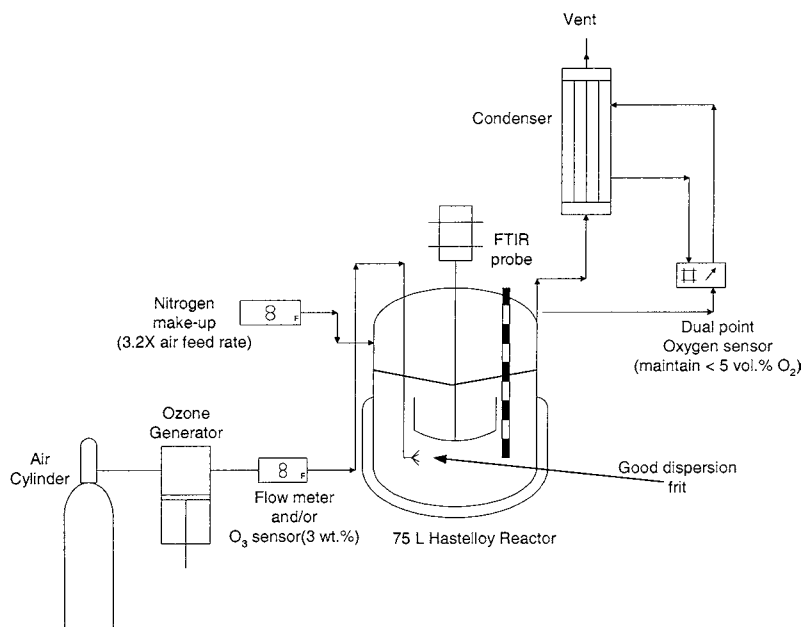


Figure 2. Schematic of the EDSF setup for the ozonolysis reaction.

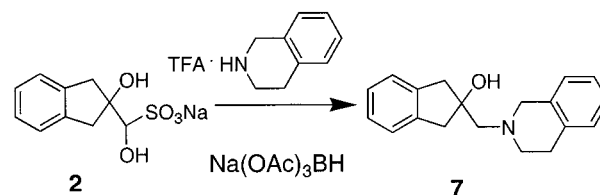
methanol vapor is 6.2–6.6% v/v in oxygen.¹⁴ Of additional note, the flash point (FP) of methanol was not significantly affected by the oxygen content: 9.8 °C in pure oxygen¹⁴ versus 11.0 °C in air.

The PSREL (Process Safety and Reaction Engineering Lab)-recommended setup, as shown in Figure 2, was to utilize air as the feed gas for the ozone generator and then with N₂ flow to dilute the headspace of the tank through two nozzles with 3.2 times the air-feed gas flow rate. This setup was determined to maintain <10% O₂-concentration in the headspace, which in turn was monitored by an oxygen detector. A “solvent run” was performed to estimate the solvent loss due to gas flow. A loss of approximately 1 L/h of acetone from an initial volume of 50 L at –70 °C was observed.¹⁵ During this solvent run the solvent vapor concentration was calculated to be 3.2% (v/v) acetone. If the same rate of solvent loss occurred in methanol, it would equate to ca. 6% (v/v) vapor concentration which is very close to the LFL. However, we expected the loss of methanol to be lower than the loss of acetone on the basis of its lower vapor pressure (5 mmHg at –40.5 °C for acetone, vs 1 mmHg at –44.0 °C for methanol).¹⁶ Additionally, during the actual ozonolysis reaction the total gas flow rate was 65–70 L/min (versus 200 L/min in the solvent run).

3. Utility of Bisulfite Adduct **2** in a Reductive Amination. Two methods for coupling bisulfite adduct **2** with

tetrahydroisoquinoline (a representative secondary amine) were identified (Scheme 6).

Scheme 6^a



^a Conditions: **Method A:** 1.0 equiv of amine and 1.5 equiv of **2**, 7 vols of NMP and 2 vols of cyclohexane, azeotropic distillation to remove cyclohexane and water (pot temperature 105 °C); cool to room temperature and add 1.5 equiv of Na(OAc)₃BH to provide, after aqueous workup and flash chromatography, a 55% yield of **7**. **Method B:** 1.0 equiv of amine and 2.5 equiv of **2** (the latter converted to aldehyde by treatment in 2-methyl-THF with 1 N NaOH, resulting in an aq pH of 10), azeotropic distillation of 2-methyl-THF to remove water, and addition of 2.0 equiv of Na(OAc)₃BH. Aqueous workup and flash chromatography provided **7** in 86% overall yield.

The first, laboratory-scale method (Method A) focused on the direct use of the bisulfite adduct, as initial attempts to break the adduct and extract free aldehyde into an organic solvent were problematic. The challenge was to identify a solvent which would dissolve both the bisulfite adduct and the tetrahydroisoquinoline–trifluoroacetic acid (TFA) salt; *N*-methylpyrrolidinone (NMP) was the only such solvent identified. Azeotropic removal of a more volatile cosolvent (cyclohexane) facilitated dehydration to the iminium species, which was rapidly reduced upon addition of Na(OAc)₃BH, providing amine **7** in 55% yield after flash chromatography. Concern with the presence of residual NMP prompted us to identify a second method (Method B), in which the bisulfite adduct was converted to free aldehyde by treatment with 1 N NaOH and 2-methyl-THF (final aq pH = 10). The tetrahydroisoquinoline–TFA salt was then added to the organic layer, solvent was distilled to azeotropically remove water, and Na(OAc)₃BH was added to effect reduction. The latter method provides an 86% yield of amine

(13) Bodurtha, G. F. *Industrial Explosion Prevention and Protection*; McGraw-Hill: New York, 1980; p 14.

(14) Data generated by Chilworth Technology, Inc. Private communication of October 13, 2000.

(15) The experiment examined the solvent loss at the maximum gas flow rate of 200 L/min of total gas flow (150 L/min nitrogen in the reactor headspace and 50 L/min of air subsurface). The tank was charged with acetone (bp 56 °C vs 65 °C for MeOH), and resulted in a solvent loss of ca. 1 L/h at –70 °C from an initial volume of 50 L. Acetone was chosen in place of methanol on the basis of its availability as a standard solvent for tank rinses and its slightly greater volatility.

(16) Perry, R. H.; Green, D. W. *Perry's Chemical Engineers' Handbook*, 6th ed.; McGraw-Hill: New York, 1984; pp 3–50 to 3–62.

7, and has been executed on 3-kg scale with a different (proprietary) amine.

Conclusions

We have described the synthesis of bisulfite adduct **2**, which serves as an easily handled surrogate for aldehyde **1** in the reductive amination shown in Scheme 6. In addition, the calorimetry, safety, and engineering issues involved with the safe execution of an ozonolysis on multikilogram scale have been described.

Experimental Section

Reagents were purchased from commercial suppliers and used as received unless otherwise noted. Laboratory-scale experiments with NMP and THF were purchased from Aldrich in anhydrous "Sure-Seal" glass bottles; all other solvents were reagent grade. Laboratory-scale reactions were run under a positive pressure of nitrogen in glassware which was flame-dried under nitrogen. Reaction progress was monitored by TLC, GC/MS, or HPLC. TLC was performed on precoated sheets of 60 F254 (Merck Art. 5719), and visualized by UV, or staining with iodine, phosphomolybdic acid, ceric ammonium molybdate, or *p*-anisaldehyde solutions and heating. GC analyses were performed on a Hewlett-Packard 6890 GC/MS with a 5973 mass selective detector. Mass spectral data were collected on either a Hewlett-Packard 6890 GC/MS (electron impact ionization) or a Micromass (Fisons) Platform II mass spectrometer (atmospheric pressure chemical ionization). Combustion analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York.

2-Vinyl-indan-2-ol (3). A 1.0 M solution of vinyl Grignard in THF (250 mL, 250 mmol) was diluted with 120 mL of toluene and concentrated in vacuo (25 mmHg, water bath at 30 °C) to remove the bulk of the THF. The resulting toluene solution was cooled to 0 °C under nitrogen, and a solution of 2-indanone (13.2 g, 100 mmol) in 65 mL of methyl-*tert*-butyl ether was added over 20 min (a suspension formed in the reaction mixture during the addition). After stirring for 30 min, the reaction was allowed to warm to room temperature. The reaction was quenched by addition of 200 mL of 1 N HCl (slow addition initially due to exothermic quench of remaining Grignard reagent). After stirring for 15 min, the organic layer was separated, washed with two 100-mL portions of water, and dried over Na₂SO₄. Filtration and concentration provided a dark-brown oil (15.0 g, 93% crude yield), which was used directly in the ozonolysis without further purification. HPLC and ¹H NMR analysis indicated ca. 95% purity. ¹H NMR (CDCl₃): δ 7.36–7.04 (m, 4H), 6.18 (dd, *J* = 11, 17 Hz, 1H), 5.42 (d, *J* = 17 Hz, 1H), 5.15 (d, *J* = 11 Hz, 1H), 3.20 (d, *J* = 16 Hz, 2H), 2.98 (d, *J* = 16 Hz, 2H). MS (EI): *m/z* 160 (M⁺, 40), 105 (100).

Sodium Hydroxy-(2-hydroxyindan-2-yl)methanesulfonate (2). The crude allylic alcohol prepared above (15.0 g, 93.6 mmol) was dissolved in 150 mL of MeOH, cooled to –78 °C, and treated with a stream of ozone generated from O₂. The dark solution became lighter in color after ca.

15 min, and HPLC analysis indicated consumption of starting material. Oxygen was bubbled through the solution for 5 min, and then a stream of nitrogen was bubbled through for 30 min. A slurry of NaHSO₃ (19.5 g, 187 mmol) in 15 mL of water was then added, and the mixture was allowed to gradually warm to room temperature. After 30 min, a starch–KI strip tested negative for peroxides. The slurry was then heated to 60 °C for 30 min to complete formation of the bisulfite adduct. After cooling to room temperature and stirring for 2 h, the resulting solids were collected and rinsed with methanol (2 × 30 mL), to provide the desired product as a white powder (16.2 g, 61% yield from 2-indanone). Combustion analysis of this material indicated 56% purity (Anal. Calcd for C₁₀H₁₁SO₅Na: C, 45.1; H, 4.2. Found: C, 25.2; H, 2.6). Recrystallization from 10 vols of water provided analytically pure material in 47% recovery (8.01 g recrystallized from 80 mL of water, isolated 3.75 g analytically pure **2**). ¹H NMR (D₂O): δ 7.15–7.12 (m, 2H), 7.08–7.04 (m, 2H), 4.46 (s, 1H), 3.30 (d, *J* = 17 Hz, 1H), 3.18 (d, *J* = 17 Hz, 1H), 2.86 (d, *J* = 8 Hz, 1H), 2.82 (d, *J* = 8 Hz, 1H). ¹³C NMR (DMSO-*d*₆): δ 143.0, 142.5, 126.43, 126.37, 125.1, 124.9, 85.8, 82.8, 45.2, 43.5. Anal. Calcd for C₁₀H₁₁SO₅Na: C, 45.1; H, 4.2. Found: C, 45.1; H, 4.1.

Scale-Up of Vinyl Grignard Addition. A clean, dry, 100-L glass-lined reactor was charged with 38 L of 1.0 M vinyl Grignard solution in THF (38 mol). Vacuum distillation was initiated (20 °C/13 mmHg) and 14 L of THF collected. A 9-L portion of toluene was charged, and vacuum distillation continued until the reactor volume reached 12 L. Another 9-L portion of toluene was added, and distillation resumed to a volume of 12 L. This solution was cooled to 0 °C and held overnight at that temperature. A solution of 2-indanone (2.0 kg, 15.1 mol) in 10 L of 1:1 MTBE–toluene was added at such a rate that the pot temperature did not rise above 0 °C (the addition required 35 min). The addition tank was rinsed with 4 L of toluene. The reactor was warmed to 25 °C over a period of 60 min, at which point analysis of an aliquot by HPLC indicated >90% conversion. The reaction mixture was quenched by the careful addition of 39 L of 1 N HCl. The quench was performed at a rate (quite slow initially, 45 min total time) such that the pot temperature did not rise above 40 °C (the jacket was set to 0 °C to provide cooling). The aqueous phase was pH 1 at the end of this quench. The layers were allowed to settle, and the lower aqueous layer was removed. The organic phase was washed with two additional 15-L portions of water (10 min stirring for each wash). The organic phase was concentrated under vacuum (30–35 °C/13 mmHg) to a volume of ca. 4 L, and the resulting product-rich solution was used directly in the next reaction (crude mass is 3.49 kg, or 144% of theory, extra weight due to residual solvent).

Scale-Up of Ozonolysis and Bisulfite Formation. A clean, dry, 75-L Hastelloy reactor (subsurface sparger for introduction of O₃, separate N₂ inlet to headspace at such a rate that gas output is 95% N₂, 65–70 L/min) was charged with 35 L of MeOH and the crude allylic alcohol prepared above (14.4 mol based on 95% yield for the previous step). The solution was cooled to a temperature of –59 °C. Ozone

generation was initiated using an Ozonia model CFS-3A ozone generator (80% output, 1600 W, flow 15–20 L/min, 4–5 wt % O₃ in air). The ozonolysis was continued for 19 h, maintaining the pot temperature between –55 to –60 °C (at 7 h an additional 9-L portion of MeOH was added to maintain the volume). After 19 h, a color change was observed (from a hazy, colorless solution to clear yellow). The solution was then purged with N₂ for 90 min and allowed to warm to 0 °C. An aliquot was quenched (aqueous NaHSO₃) and analyzed by HPLC, which showed no remaining starting material. The reaction solution (at 0 °C) was then transferred to a second 75-L glass-lined reactor containing NaHSO₃ (3.0 kg, 28.8 mol) and 6 L of water. The transfer was performed at a rate such that the pot temperature did not exceed 0 °C (transfer required 30 min). Two liters of MeOH were used to rinse the original reactor. The resulting slurry was stirred and allowed to warm to 25 °C over 90 min, at which point a KI/starch indicator strip indicated no peroxides present (DSC analysis of an aliquot also indicated absence of high-energy intermediates). The slurry was then warmed to 55–60 °C, and a partial vacuum (290 mmHg) was applied to remove MeOH (15 L were collected). The slurry was then cooled to 25 °C and stirred for 15 h. The resulting solids were collected by filtration, rinsing with MeOH. After drying in a vacuum oven under a stream of N₂, 2.89 kg of a white to off-white solid were obtained. Karl Fischer analysis indicated 0.65% H₂O. Elemental analysis: C 34.0, H 3.18. C₁₀H₁₁SO₅Na requires C 45.1, H 4.2, indicating ca. 75% purity, with 25% residual inorganics. This material was suitable for use in the following reductive amination, or could be recrystallized from aqueous EtOH as described above.

Representative Reductive Amination: 2-(3,4-Dihydro-1H-isoquinolin-2-ylmethyl)-indan-2-ol (7). **Method A.** Tetrahydroisoquinoline (0.39 mL, 3.13 mmol) and 15 mL of NMP were cooled to 0 °C. TFA (0.24 mL, 3.13 mmol, 1.0 equiv) was added, followed by bisulfite adduct **2** (1.25 g, 4.70 mmol, 1.5 equiv). Five milliliters of cyclohexane was added, and the reaction flask fitted with a short-path distillation head. The mixture was heated in a 90 °C oil bath and the water–cyclohexane azeotrope collected at 68–70 °C head temperature. The oil bath was gradually increased to 105 °C, at which point the reaction mixture was homogeneous, and the distillation ceased. The solution was then cooled to 25 °C and treated with NaBH(OAc)₃ in a single portion (1.00 g, 4.70 mmol, 1.5 equiv). The resulting slurry was stirred overnight, at which point MS analysis indicated complete conversion of the tetrahydroisoquinoline to **7**. The reaction was quenched with water, made basic with

20% aqueous Na₂CO₃, and extracted with ethyl acetate. Flash chromatography with 5:1 hexanes–ethyl acetate provided the desired product as a colorless oil, which solidified upon standing: 0.48 g, 1.72 mmol, 55% yield.

Method B. Bisulfite adduct **2** (1.00 g, 3.76 mmol, 2.5 equiv) was suspended in 10 mL of water and 10 mL of 2-methyl-THF. NaOH (1 N) was added dropwise until the aqueous phase reached pH 10 (3.0 mL were required). The resulting two-phase mixture was transferred to a separatory funnel and diluted with ca. 5 mL of 2-methyl-THF and 10 mL of water. The aqueous phase was removed and the organic phase washed with two portions of 20% aqueous Na₂CO₃. The resulting organic solution was transferred to a two-neck round-bottom flask, and concentrated via atmospheric distillation to a volume of ca. 12 mL. In a separate flask, tetrahydroisoquinoline (0.188 mL, 1.50 mmol, 1.0 equiv) was dissolved in 2 mL of 2-methyl-THF and treated with trifluoroacetic acid (0.116 mL, 1.50 mmol, 1.0 equiv), then added to the aldehyde solution. Atmospheric distillation was resumed until the volume was reduced from 15 mL to ca. 10 mL. The solution was cooled to room temperature and treated with NaBH(OAc)₃ in a single portion (0.64 g, 3.0 mmol, 2.0 equiv). After stirring overnight, MS analysis indicated complete consumption of tetrahydroisoquinoline. The reaction was quenched with water and made basic with 20% aqueous Na₂CO₃, and the phases were separated. The organic phase was washed with brine, dried over Na₂SO₄, filtered, and concentrated to provide 0.64 g of crude product. Flash chromatography (5:1 hexanes–ethyl acetate) provided the product **7** as a colorless oil: 0.360 g (1.29 mmol, 86% yield). IR (thin film) 3424 (br), 3201, 2898, 2796, 1584, 1481, 1425, 1307, 1133, 1087, 737 cm⁻¹. ¹H NMR (CDCl₃): δ 7.25–7.03 (m, 8H), 3.88 (s, 2H), 3.05 (s, 4H), 2.99–2.95 (m, 4H), 2.83 (s, 2H). ¹³C NMR (CDCl₃): δ 141.4, 134.9, 134.3, 129.0, 126.7, 126.6, 126.0, 125.0, 124.9, 80.3, 66.1, 57.6, 52.9, 46.7, 29.4. MS (CI): *m/z* 280 (M + 1, 100). Anal. Calcd for C₁₉H₂₁NO: C, 81.7; H, 7.6. Found: C, 81.7; H, 7.5.

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