Selective synthesis of 3-hydroxy acids from Meldrum's acids using SmI_2-H_2O

Michal Szostak, Malcolm Spain & David J Procter

School of Chemistry, University of Manchester, Manchester, UK. Correspondence should be addressed to D.J.P. (david.j.procter@manchester.ac.uk).

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The single-step synthesis of 3-hydroxy carboxylic acids from readily available Meldrum's acids involves a selective monoreduction using a SmI_2-H_2O complex to give products in high crude purity, and it represents a considerable advancement over other methods for the synthesis of 3-hydroxy acids. The protocol includes a detailed guide to the preparation of a single electron–reducing SmI_2-H_2O complex and describes two representative examples of the methodology: monoreduction of a fully saturated Meldrum's acid (5-(4-bromobenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione) and tandem conjugate reduction-selective monoreduction of α,β-unsaturated Meldrum's acid (5-(4-methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione). The protocol for selective monoreduction of Meldrum's acids takes ~6 h to complete.

INTRODUCTION

3-Hydroxy acids are important building blocks and intermediates in the pharmaceutical, chemical and polymer industries[1–19]. In particular, they have been recognized for their application in medicinal chemistry as anti-inflammatory agents[5,6]. As close isosteres of salicylic acid, 2-aryl-3-hydroxy acids have attracted considerable attention in drug discovery programs[7,8]. In organic synthesis, 3-hydroxy acids are key intermediates in the assembly of functionalized derivatives of carboxylic acids bearing heteroatoms in the β position[9–13]. 3-Hydroxy acids have also been exploited as vital components in antiaging applications in cosmetics and dermatology[14,15]. Recently, the simplest member of this compound class, 3-hydroxy propionic acid, has been used as a precursor to highly promising biodegradable polymers with downstream application in the plastic industry as nontoxic replacement for polyester[16–19]. Nevertheless, the short, selective synthesis of 3-hydroxy acids remains a challenge in organic chemistry[20,21].

Since its introduction to the global synthetic community in 1977 (ref. 22), samarium diiodide (SmI_2, Kagan's reagent) has become the most versatile and convenient-to-use electron transfer reagent available in organic synthesis[23–32]. SmI_2 promotes reactions that proceed through open-shell, single-electron pathways that offer alternative reaction outcomes to transformations that proceed through closed-shell, two-electron mechanisms. Crucial to the versatility of SmI_2 is the use of additives to tune and modify its properties[33,34]. Our group has pioneered the use of water as an environmentally benign additive for use with SmI_2. The resulting SmI_2-H_2O complex is characterized by unprecedented properties arising from the high affinity of the samarium center for water and has led to a dramatic expansion of reactions promoted by SmI_2 (ref. 35). Of particular note is the exceptional functional group tolerance, selectivity, nontoxic properties and the operational ease of use of the SmI_2-H_2O reagent, all of which compare favorably with other single-electron transfer reagents and SmI_2-based systems.

Recently, we reported[36] a mild procedure for the single-step synthesis of 3-hydroxy acids (**2**) from Meldrum's acids[37–40] (**1**) using the SmI_2-H_2O complex (**Fig. 1**). Furthermore, we found that α,β-unsaturated intermediates (**3**), readily produced in the reaction of Meldrum's acid with aldehydes, underwent sequential conjugate reduction and selective monoreduction in the presence of SmI_2-H_2O, providing a general method for the synthesis of 3-hydroxy carboxylic acids. Subsequently, we have demonstrated novel reactivity of other functional groups using SmI_2-H_2O[41–46]. Mechanistically, these reactions proceed via single-electron reduction of carbonyl groups to generate unusual ketyl radical intermediates stabilized in the cyclic six-membered ring system by anomeric effects resulting from the two neighboring oxygen atoms[43,44].

A conventional route to 3-hydroxy carboxylic acids from Meldrum's acids involves multiple steps: conversion to the monoacid, activation of the monoacid as a mixed anhydride, reduction and hydrolysis[47]. It is also important to note that the preparation of 3-hydroxy carboxylic acids using formaldehyde aldol reactions is challenging. Our protocol allows the transformation of Meldrum's acids to 3-hydroxy carboxylic acids to be achieved in a single step using SmI_2-H_2O. Moreover, in combination with the Knovenagel condensation between aromatic aldehydes and Meldrum's acid, the process using SmI_2-H_2O allows for streamlined preparation of 3-hydroxy carboxylic acids for use in industrial and academic environments.

Experimental design

Here we describe synthetic procedures for the formation of 3-hydroxy acid (**6**) (2-(4-bromobenzyl)-3-hydroxypropanoic acid) and (**8**) (3-hydroxy-2-(4-methoxybenzyl)propanoic acid) (**Fig. 2**) as representative examples of a general method for the synthesis of 3-hydroxy carboxylic acid derivatives by the SmI_2-H_2O-mediated reduction of fully saturated and α,β-unsaturated Meldrum's acids. Both starting materials can be readily

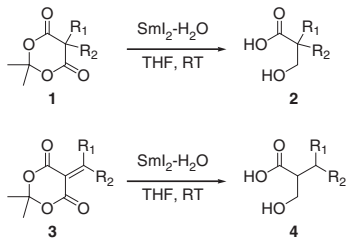


Figure 1 | Single-step synthesis of 3-hydroxy carboxylic acids from Meldrum's acid derivatives using SmI_2-H_2O. RT, room temperature (23 °C).

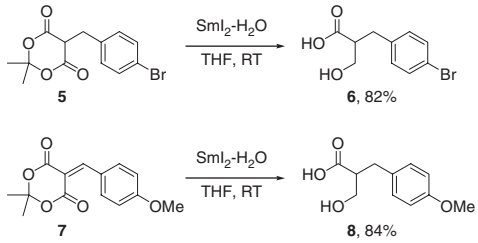


Figure 2 | Scheme for the synthesis of 2-(4-bromobenzyl)-3-hydroxypropanoic acid (**6**) and (3-hydroxy-2-(4-methoxybenzyl)propanoic acid) (**8**).

prepared in one or two steps from commercially available materials and purified by crystallization[48,49].

The protocol can be readily performed on larger or smaller scales uses commercial reagents, simple procedures and purifications. The first step describes the preparation of SmI_2-H_2O complex using samarium metal and 1,2-diiodoethane to synthesize SmI_2, followed by the addition of water to form the active complex. We note that although commercially available SmI_2 is not ideal for use in this chemistry due to the high content of samarium triiodide, we found that other methods of preparation of SmI_2 (for example, Imamoto's method[50–52] using iodine and samarium metal) are equally efficient.

The SmI_2-H_2O system is compatible with a variety of functional groups, which are typically reactive to other reducing agents that operate through radical and anionic pathways[35,36,41–46]. Consequently, this protocol has been extended to the synthesis of a range of 3-hydroxy acids with different substituents and substitution patterns (**Fig. 3**). Aliphatic, aromatic, sterically hindered, cyclic, benzylic, and heteroatom- and ester-containing substrates were found to perform well in this reaction. As the cyclic nature of substrates (see **1** and **3**, **Fig. 1**) is required for the reduction, no over-reduction is observed even in the presence of excess SmI_2-H_2O. Conveniently, α,β-unsaturated Meldrum's acids react at a comparable rate to fully saturated analogs, thereby facilitating the synthesis of substituted 3-hydroxy acids. Notably, a large excess of

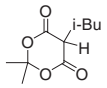
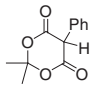
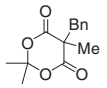
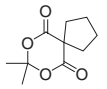
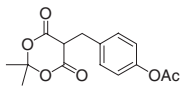
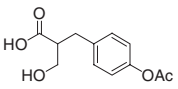
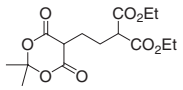
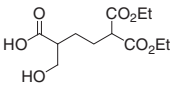
Entry	Meldrum's acid	3-Hydroxy acid	Yield (%)
1			94
2			72
3			98
4			81
5			67
6			78

Figure 3 | Representative examples of 3-hydroxy carboxylic acids synthesized from cyclic 1,3-diesters using SmI_2-H_2O.

water co-solvent is necessary for the reduction and no reaction is observed when other proton sources are used.

Although SmI_2 is oxygen-sensitive and all operations involving this reagent should be performed using standard Schlenk techniques[53], we have determined that in the reduction of Meldrum's acids with SmI_2-H_2O simple degassing techniques involving sparging of reaction vessels and solvents with inert gas give comparable results, thus greatly increasing the simplicity and user-friendly nature of the protocol.

MATERIALS

REAGENTS

- Samarium metal (−40 mesh; Acros Organics, cat. no. 294780500; stored at room temperature (23 °C) in air; approximate price, 50 g = €200–300)
- 1,2-Diiodoethane (stored at 2–8 °C; Aldrich, cat. no. D122807)
- Diethyl ether (ACS reagent grade; Sigma-Aldrich, cat. no. 32203)
- Sodium thiosulfate (pentahydrate; Fisher Scientific, cat. no. S445-3)
- Tetrahydrofuran (THF, anhydrous, >99.9%; Sigma-Aldrich, cat. no. 186562)
- Deionized water (Fluka, cat. no. 99053)
- 5-(4-Bromobenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**5**, prepared according to ref. 48, http://pubs.acs.org/doi/suppl/10.1021/jo900390d/suppl_file/jo900390d_si_001.pdf)
- 5-(4-Methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**7**, prepared according to ref. 48, http://pubs.acs.org/doi/suppl/10.1021/jo900390d/suppl_file/jo900390d_si_001.pdf)
- Triethylamine (anhydrous; Sigma-Aldrich, cat. no. 471283)
- Cyclohexanone (Aldrich; cat. no. W390909)
- Dichloromethane (HPLC grade; Sigma-Aldrich, cat. no. 34856)
- Hydrochloric acid (laboratory grade; Fisher Scientific, cat. no. H/1150/PB17)
- Sodium sulfate (anhydrous; Fisher Scientific, cat. no. S/6600/53)
- Ethyl acetate (ACS reagent grade; Sigma-Aldrich, cat. no. 33211)
- Hexane (HPLC grade; Sigma-Aldrich, cat. no. 34859)
- Acetic acid (analytical grade; Fisher Scientific, cat. no. A/0400/PB17)
- Silica gel (Aldrich, cat. no. 717185)
- Chlorofom-d_3 (Aldrich, cat. no. 151823)

EQUIPMENT

- Round-bottomed flasks (NS 24/29 single neck; Smith Scientific, Glassco, 3 × 500 ml, 1 × 250 ml, 2 × 100 ml, 1 × 50 ml)
- Screw cap vials (3 inches × 3/4 inches; Scientific Glass Laboratories, cat. no. FWF3-4)
- Separatory funnel (1 liter; Smith Scientific)
- Erlenmayer flasks (1 × 500 ml, 2 × 1 liter; Smith Scientific)
- Magnetic stir bars (egg-shaped magnetic stir bars, 38 × 16 mm; Fisher Scientific, cat. no. 22-362-715; magnetic followers 12 × 3 mm, cat. no. FB55930)
- Rubber septa (red septum stoppers, 24/40-24/25, Chemglass, cat. no. CG-3022-08; red turnover stoppers no. 25, Fisher Scientific, cat. no. FB57876)
- Needles (BD Microlance 3, 18 G × 1 1/2, 1.2 mm × 40 mm, BD Microlance, cat. no. 304622; 100 Sterican, 21 G × 4 3/4, 0.80 × 120 mm, Braun, cat. no. 2127)
- Disposable syringes (NORM-JECT, polypropylene, 1, 3, 24 and 60 ml; Sigma-Aldrich, cat. nos. Z230723, Z116858, Z116882, Z118400)
- Assorted spatulas (Fisher Scientific)
- Stirring plates (IKA RCT basic, IKA RH basic 2)
- Laboratory balance (Sartorius BP61S, 13006971)

- Rotary evaporator (Büchi R-200, Stuart RE 300; Stuart)
- Argon cylinder (BOC Pureshield Argon)
- Double manifold connected to argon line (glassblowing shop, University of Manchester)
- Vacuum pump (Edwards, RV5)
- Vacuum tubing (red nat. tubing, 6.3 inner diameter × 12.7 outer diameter, Fisher Scientific, cat. no. FB50733)
- Heat gun (Steinel, HL 1610S)
- Oven (Hotbox oven size 2, Gallenkamp)
- CAMPINGAZ (Butane/propane mixture, CG 3500)
- Filter paper (circles 24.0 cm; Whatman, cat. no. 1001-240; circles 110 mm; Whatman, cat. no. 1001-110)
- Parafilm (laboratory film, 2 inch × 250 foot roll, Pechiney Plastic Packaging)
- Aluminum foil (45 cm, Aluchef foil, Terinex)
- TLC plates (TLC silica gel 60, Merck, cat. no. 105553)
- Pasteur pipettes (glass 230 mm, Fisher Scientific, cat. no. FB50253)
- Chromatographic column (NS 12.5 × 15 mm, Springham)
- Test tubes (Pyrexengland)
- NMR tubes (Norell 502)
- Disposable gloves (AQL 1.5, Semperguard), lab coat, protective glasses (Uvex, Astrospec)

EQUIPMENT SETUP

Argon lines To set up argon lines, cut the end of a barrel of a disposable 1-ml syringe at the 1.0-ml mark, wrap the wide end with a single layer of Parafilm (approximately 2.5 × 8 cm), insert the barrel into a line connected to a double manifold and secure the barrel with a metal clip. Equip the barrel with a needle (18 G), open the tap on the double manifold to flow argon though the line and insert the needle into the required vessel. Alternatively, nitrogen can be used in place of argon.

Flushing vessel To set up a flushing vessel, equip a 4-dram vial with a septum, insert the argon line (prepared as described above), open the line to vacuum for ~30 s and backfill with argon. Repeat the backfilling cycles two times and leave the vessel under a positive pressure of argon.

Flushing syringes with argon To flush syringes with argon, insert a syringe equipped with a needle into the flushing vessel, pull up the plunger to fill the syringe with argon and open the tap on the double manifold to vacuum (this will cause the plunger to collapse back into the barrel). Next, open the tap on the double manifold to argon, pull the plunger to fill the syringe with argon and repeat the cycles two more times. After the final cycle fill the syringe with argon and expel the gas immediately prior to using the syringe. ▲ **CRITICAL** All syringes used in the protocol should be subjected to the flushing procedure.

Preparing glassware All glassware used in the protocol should be dried in the oven operating at 140 °C (or higher temperature) for at least 24 h or flame-dried directly before use when indicated.

REAGENT SETUP

Degassing solvents To degas solvents, equip a vessel (a vial or 100-ml round-bottomed flask) with a septum, wrap the septum with Parafilm to ensure an air-free atmosphere and then insert the argon line into the vessel as described in the EQUIPMENT SETUP. Evacuate/backfill the vessel with argon three times, transfer the required solvent under positive pressure of argon and then insert a venting needle (18 G) into the septum. Immerse the needle (21 G) with a positive pressure of argon into the solvent and increase the pressure of argon until bubbling appears (**Fig. 4**). After 10–15 min, the solvent is ready to use. ▲ **CRITICAL** All solvents used for the manipulation of SmI_2 solutions should be subjected to the degassing procedure. Other degassing methods (for example, freeze-pump-thawing or distillation under inert gas) can also be used but are more time-consuming.

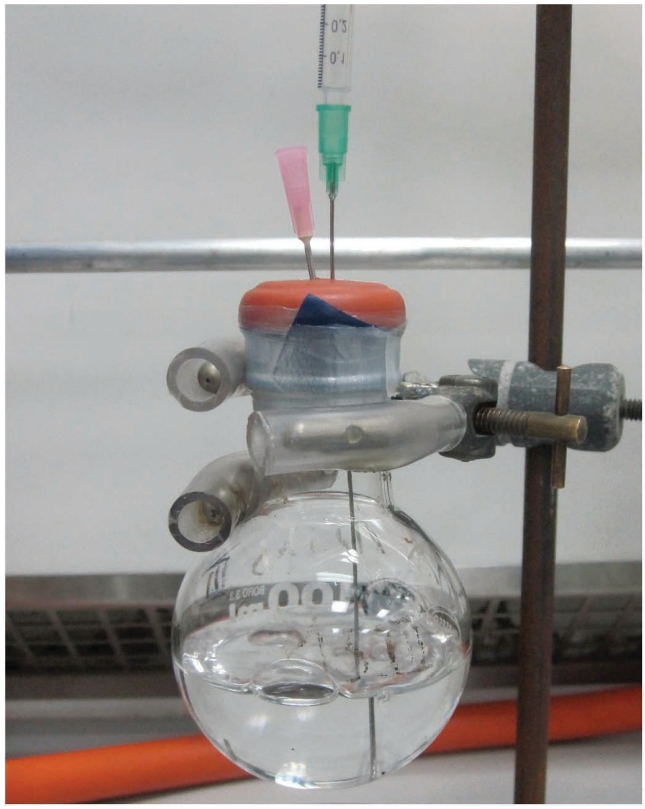


Figure 4 | Typical solvent degassing setup. Note that the inlet needle (green, 21 G) is at the bottom of the flask and the outlet needle (pink, 18 G) is near the top of the flask.

PROCEDURE

! CAUTION All manipulations should be performed inside a well-ventilated fume cupboard. Protective equipment (protective glasses, gloves, lab coat) should be used for the handling of all chemicals and solvents. Aqueous and solid waste should be disposed of according to standard protocols.

Preparation of SmI_2

1| Weigh 20 g of 1,2-diiodoethane into a 500-ml round-bottomed flask.

2| Add ~400 ml of diethyl ether and dissolve the 1,2-diiodoethane by gentle swirling.

3| Transfer the solution of 1,2-diiodoethane into a 1,000-ml separatory funnel.

4| Wash the diethyl ether layer with 100 ml of aqueous saturated sodium thiosulfate solution (prepared by dissolving 100 g of sodium thiosulfate in 500 ml of water).

5| Repeat the washing with 100-ml portions of aqueous saturated sodium thiosulfate solution four more times.

6| Wash the diethyl ether layer with 100 ml of water.

7| Dry the diethyl ether layer over 50 g of sodium sulfate in a 500-ml Erlenmeyer flask.

8| Filter the diethyl ether layer into a 250-ml round-bottomed flask using filter paper and a polypropylene funnel. Alternatively, a G4 frit and vacuum can be used, although this method is more time consuming.

9| Concentrate the filtrate on a rotary evaporator to yield a white solid. Steps 1–9 can be carried out in air.
▲ **CRITICAL STEP** Commercial 1,2-diiodoethane is contaminated with iodine and should be purified by washing with sodium thiosulfate to yield a fluffy white solid.

10| Equip the 250-ml flask with a rubber septum and needle (18 G), wrap the flask in aluminum foil and place it under high vacuum for ~30 min.
▲ **CRITICAL STEP** 1,2-Diiodoethane should be thoroughly dried before use to ensure fast activation of the samarium metal surface. 1,2-Diiodoethane is light sensitive and should be stored with the exclusion of light. We recommend fresh purification of 1,2-diiodoethane for every preparation of SmI_2.

11| Flame-dry a 500-ml round-bottomed flask equipped with a Teflon-coated magnetic stir bar (38 × 16 mm) and septum (24/40-24/25) under vacuum (see EQUIPMENT SETUP). Allow the flask to cool to room temperature, backfill with argon and repeat the evacuation/backfilling cycles three times. After the final cycle leave the flask under a positive pressure of argon.

12| Weigh 12.0 g of samarium metal into a vial and add it to the flame-dried 500-ml round-bottomed flask by removing the septum and quickly adding the samarium metal from the vial.

13| Weigh 11.28 g of 1,2-diiodoethane into a vial and add it to the same flame-dried 500-ml round-bottomed flask by removing the septum and quickly adding the 1,2-diiodoethane from the vial.

14| Seal the 500-ml round-bottomed flask around the septum using Parafilm to ensure an air-free atmosphere.

15| Carefully subject the flask to three evacuation/backfilling cycles with argon, and start stirring at the medium speed.

16| Transfer 400 ml of THF to the 500-ml round-bottomed flask containing samarium metal and 1,2-diiodoethane using multiple 60 ml syringes.
▲ **CRITICAL STEP** Approximately 2–3 min after addition of the first portion of THF, the color changes from metallic to green-blue, indicating that samarium triiodide and SmI_2 start to form. At this point, evacuate/backfill with argon three to five times to remove ethylene and facilitate the synthesis of SmI_2. (Ethylene is formed during the insertion of samarium metal into 1,2-diiodoethane.)

17| After the transfer of the final portion of THF, evacuate/backfill three times to remove the final portions of ethylene.

18| (Optional) Remove the argon line and seal the septum using Parafilm to ensure an air-free atmosphere. This step can be omitted if the reaction is stirred under a positive pressure of argon.

19| Stir the solution at room temperature for 18 h to yield a deep-blue solution of SmI_2 (**Fig. 5a**).
? TROUBLESHOOTING

20| Turn off the stirring and allow the solution of SmI_2 to settle for 30 min.
▲ **CRITICAL STEP** SmI_2 is air-sensitive. Remember to perform all manipulations involving SmI_2 under a strong flow of argon. Although it is by no means necessary, it is also convenient to carry out all operations in standard Schlenk glassware.

21| Titrate the solution of SmI_2 according to ref. 51. Alternatively, iodometric titration can be used, according to ref. 52.
■ **PAUSE POINT** Solutions of SmI_2 can be stored over a period of 1 month when kept under inert atmosphere[54].

Synthesis of 3-hydroxy carboxylic acids
▲ **CRITICAL** Perform the preparation of 3-hydroxycarboxylic acids using SmI_2 and with reference to the table in Step 23.

22| Flame-dry a 500-ml round-bottomed flask equipped with a Teflon-coated magnetic stir bar (38 × 16 mm) and septum (24/40-24/25) under vacuum (see EQUIPMENT SETUP). Allow the flask to cool to room temperature, backfill it with argon and repeat evacuation/backfilling cycles three times. After the final cycle, leave the flask under a positive pressure of argon and seal the septum with Parafilm to ensure an oxygen-free atmosphere.

23| Depending on the starting material you are using (Options A and B in the in-text table), transfer the appropriate amount of SmI_2 (prepared as described above) using 60-ml syringes and start stirring at medium speed.

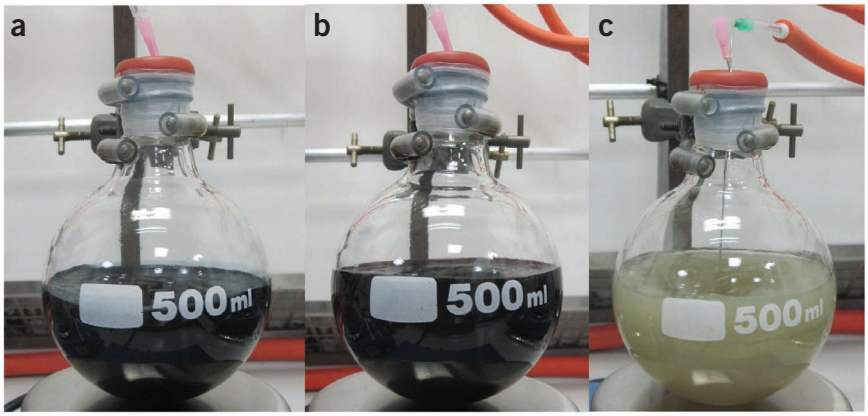


Figure 5 | Photograph of the reaction course. (**a**) Solution of SmI_2 in THF (note the characteristic blue color). (**b**) Solution of SmI_2-H_2O complex (note the characteristic burgundy red color). (**c**) Quenched reaction mixture (note that the argon line has been replaced by a venting needle and air is being bubbled through the reaction mixture).

Option	Starting material	Amount of starting material	Reagent
A	5-(4-Bromobenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**5**)	0.783 g	SmI_2 (0.076 M), 197 ml
B	5-(4-Methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**7**)	0.656 g	SmI_2 (0.075 M), 267 ml

▲ **CRITICAL STEP** SmI_2 and SmI_2-H_2O complex are oxygen-sensitive. To ensure high yields, we recommend fresh preparation of SmI_2 for every procedure.

24| Weigh the appropriate amount of the Meldrum's acid into a vial and transfer it to a 50-ml round-bottomed flask. Fit a septum (24/40-24/25), seal the septum with Parafilm to ensure an oxygen-free atmosphere and then insert the argon line. Evacuate/backfill the flask with argon three times.

25| Degas ~50 ml of deionized water using a 100-ml round-bottomed flask (see REAGENT SETUP).

26| Degas ~50 ml of THF using a 100-ml round-bottomed flask (see REAGENT SETUP).

27| Dissolve the preweighed Meldrum's acid in 20 ml of freshly degassed THF.
▲ **CRITICAL STEP** Gentle heating with a heat gun might be necessary to quickly dissolve the substrate.

28| Transfer 45 ml of freshly degassed deionized water into a 60-ml syringe and leave the tip of the needle in the 100-ml round-bottomed flask containing degassed water under argon.
▲ **CRITICAL STEP** All syringes used in the protocol should be flushed with argon before use (see EQUIPMENT SETUP).

29| Transfer the Meldrum's acid dissolved in 20 ml of THF into a 24-ml syringe and leave the tip of the needle in the 50-ml round-bottomed flask containing the substrate under argon.

30| Add 45 ml of degassed deionized water from the 60-ml syringe to the SmI_2 solution over 10–15 s while maintaining the stirring at the medium speed. The addition of water results in a characteristic color change from deep blue (SmI_2) to burgundy red, indicating the formation of SmI_2-H_2O complex (**Fig. 5a,b**).
? TROUBLESHOOTING

31| Add the Meldrum's acid dissolved in 20 ml of THF to the SmI_2-H_2O complex dropwise over 30 s. Rinse the 50-ml round-bottomed flask containing the substrate with 3 ml of THF and add the rinse to the reaction mixture.

32| Stir the reaction mixture for 15 min under argon.
? TROUBLESHOOTING

33| Remove the argon line, insert a venting needle (18 G) and bubble air through the solution using a 21-G needle until decolorization occurs to yield a milky-white suspension (**Fig. 5c**).
▲ **CRITICAL STEP** Ensure that the flow of air does not overpressurize the reaction vessel, which might result in a mechanical loss of the reaction mixture. Depending on the pressure of air, this step takes approximately 1–2 min.
? TROUBLESHOOTING

34| Transfer the quenched reaction mixture to a 1,000-ml separatory funnel and rinse the 500-ml round-bottomed reaction flask with 400 ml of dichloromethane to ensure quantitative transfer.

35| Add 500 ml of 1.0 M hydrochloric acid to the separatory funnel.

36| Extract the aqueous layer with dichloromethane. Layers separate immediately.

37| Repeat the extraction of the aqueous layer using dichloromethane (5 × 250 ml).

38| Dry the combined organic layers over 100 g of sodium sulfate and filter.
■ **PAUSE POINT** The reaction mixture can be left overnight at room temperature.

39| Concentrate the organic layers using a rotary evaporator to yield the crude product as a brown oil.

40| Purify the residue by flash chromatography on silica gel (glass column, 3.5 cm × 20 cm volume of silica gel, dry loading) using the following gradient: 10:1 hexanes/ethyl acetate (500 ml), 1:1 hexanes/ethyl acetate (300 ml, including 0.033% of HOAc), ethyl acetate (400 ml, including 0.033% of HOAc) and collecting the fractions into 15-ml test tubes.

41| Identify the fractions containing the 3-hydroxypropanoic acid corresponding to the starting material introduced in Step 23 (in-text table below, see also ANTICIPATED RESULTS) using thin-layer chromatography (1,000:1 EtOAc/HOAc); combine and concentrate the fractions to yield the title compound as a solid.
? TROUBLESHOOTING

Option	3-Hydroxypropanoic acid	Expected yield (%)
A	2-(4-Bromobenzyl)-3-hydroxypropanoic acid (**6**)	82
B	3-Hydroxy-2-(4-methoxybenzyl)propanoic acid (**8**)	84

? TROUBLESHOOTING
Troubleshooting advice can be found in **Table 1**.

TABLE 1 | Troubleshooting table.

Step	Problem	Possible reason	Solution
19	Failure to form blue color during synthesis of SmI_2	Wet reagents or glassware; oxygen in the reaction flask; samarium metal unsuitable for preparation of SmI_2	Repeat the synthesis of SmI_2 using fresh reagents. Make sure that the oxygen content is minimized; use samarium metal −40 mesh
30	Failure to form SmI_2-water complex (burgundy-red color)	Oxygen in the system; high concentration of samarium triiodide	Repeat the synthesis of SmI_2. Prepare fresh SmI_2-H_2O complex, taking extra care to exclude oxygen
32, 33	Fast decolorization of SmI_2-H_2O complex	Oxygen in the system; high concentration of samarium triiodide	Repeat synthesis of SmI_2. Prepare fresh SmI_2-H_2O complex, taking extra care to exclude oxygen
41	Low yield	Incomplete conversion	Prepare fresh SmI_2; titrate SmI_2
		Incomplete extraction of the 3-hydroxy acid from aqueous layer	Check the aqueous layer by TLC; extract the aqueous layer with extra portions of dichloromethane
		Mechanical loss	Repeat the reaction, taking extra care to ensure minimal loss of material; hydroxy acids interact with silica gel, so use acetic acid co-solvent during chromatographic purification

● TIMING

Steps 1–18, 1–2 h
Step 19, 18 h
Steps 20–33, 2 h
Steps 34–39, 1–2 h
Steps 40–41, 1–2 h

ANTICIPATED RESULTS

Typical yields

Very good yields can be expected for the reduction of Meldrum's acids with SmI_2-H_2O. In our hands, the above procedures proved to be reliable for a wide range of Meldrum's acid derivatives (average isolated yield of 80%; **Fig. 3**). Notably, using this protocol we have never observed products of over-reduction.

Analytical data

Synthesis of (6), 2-(4-bromobenzyl)-3-hydroxypropanoic acid

White solid (m.p. = 84–86 °C), 528 mg, 82%.
TLC (1,000:1 EtOAc/HOAc): R_f=0.27. Visualized using $KMnO_4$.
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.72–2.80 (m, 2H), 2.88–2.96 (m, 1H), 3.61–3.65 (m, 1H), 3.70–3.74 (m, 1H), 7.01 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 6.5–7.5 (1H, br).
^{13}C NMR (125 MHz, $CDCl_3$): δ 33.3, 48.7, 61.8, 120.6, 130.7, 131.7, 137.2, 179.4.
IR (neat, cm^{-1}): 3,333, 2,944, 2,603, 1,693, 1,489, 1,403, 1,346, 1,293, 1,244, 1,207, 1,166, 1,112, 1,097, 1,061, 1,013, 951, 929, 906, 843, 832, 795, 764, 714.
MS (ES) m/e calculated for $C_{10}H_{11}O_3BrNa$: (M^+ + 23) 280.9784, found 280.9780.

Synthesis of (8), 3-hydroxy-2-(4-methoxybenzyl)propanoic acid

White solid (m.p. = 80–82 °C), 442 mg, 84%.
TLC (1,000:1 EtOAc/HOAc): R_f = 0.36. Visualized using $KMnO_4$.
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.81–2.90 (m, 2H), 2.99–2.08 (m, 1H), 3.72–3.77 (m, 1H), 3.79–3.83 (m, 1H), 3.81 (s, 3H), 6.86 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 33.2, 49.0, 55.3, 61.9, 114.0, 130.0, 130.2, 158.3, 179.7.
IR (neat, cm^{-1}): 3,415, 3,335, 2,908, 2,611, 1,695, 1,612, 1,513, 1,470, 1,414, 1,349, 1,298, 1,246, 1,219, 1,177, 1,113, 1,060, 1,034, 1,004, 930, 906, 841, 802, 770.
MS (ES) m/e calculated for $C_{11}H_{14}O_4Na$: (M^+ + 23) 233.0785, found 233.0786.

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