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A practical synthesis of a [2.2.1] bicyclic chiral sulfide for asymmetric transformations

Varinder K. Aggarwal,* Guangyu Fang, Christoforos G. Kokotos, Jeffery Richardson and Matthew G. Unthank

Department of Chemistry, University of Bristol, Cantock's Close, Bristol, United Kingdom

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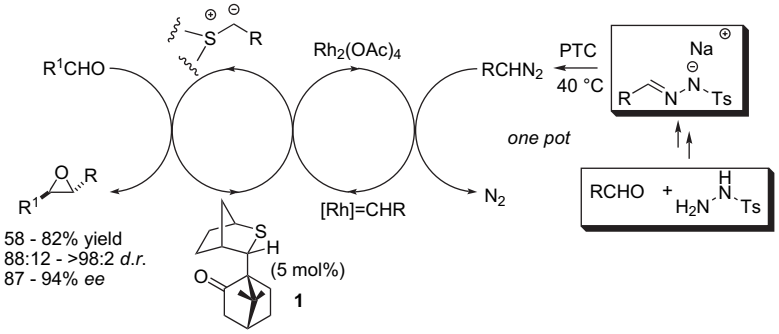
This paper is dedicated to Professor David MacMillan, the rising star of our generation

Abstract—A substantially improved synthesis of synthetically useful chiral sulfide **1** is described. Starting from (+)-10-camphorsulfonic acid, the chiral sulfide was synthesised on large scale in five steps and 56% overall yield. Significant improvements include the use of Bu_3P in place of Ph_3P for the reduction of the chlorosulfonyl group to the thiol, allowing removal of phosphine oxide by aqueous extraction and improvements in the photochemistry using either a modified batch reactor or a single pass continuous flow reactor.

1. Introduction

Sulfur ylides are extremely useful carbon nucleophiles in organic synthesis.[1] They are mostly used for two types of reactions: three-membered ring formation (epoxidation, cyclopropanation or aziridination) and rearrangement reactions.[2] In the first class of reactions the sulfur ylide reacts with an electrophilic carbon atom (of a carbonyl group, imine or an activated carbon–carbon double bond) followed by elimination of the sulfide to give a strained three-membered ring. We have developed a new catalytic process in which tosyl hydrazone salts couple with carbonyl compounds to give epoxides with control over relative and absolute stereochemistry in high yield (Scheme 1). The reaction is mediated by sub-stoichiometric quantities of a chiral sulfide (5 mol %) and rhodium acetate (0.5 mol %).[3] The process shows good substrate scope but with many catalytic process limitations. As a result of these limitations, we have developed a stoichiometric epoxidation protocol, which is highly efficient and enantioselective and shows very broad substrate scope.[4]

The catalytic process has been extended to the synthesis of cyclopropanes and aziridines (Scheme 2).[5] The practicality of these processes has been demonstrated in the synthesis of a number of biologically important targets (CDP 840,[5] prelactone B,[6] taxol side chain,[7] and the anti-hypertensive agent (+)-LY354740[8]) involving each class of three-membered ring compounds with almost complete control of chirality.



Scheme 1. Catalytic cycle for epoxide formation with in situ generation of diazocompounds.

* Corresponding author. Tel.: +44 117 954 6315; fax: +44 117 929 8611; e-mail: v.aggarwal@bristol.ac.uk

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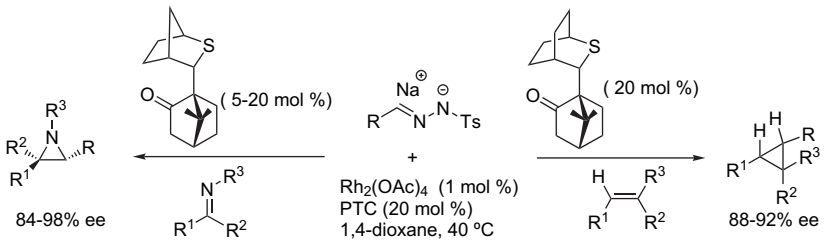
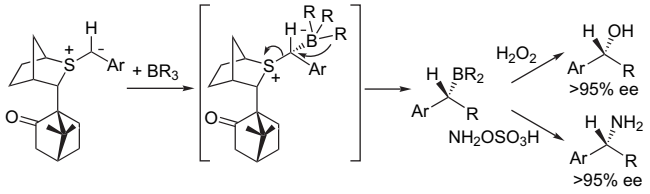


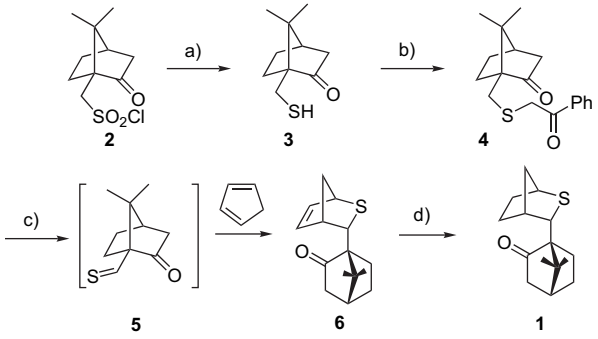
Scheme 2. Catalytic asymmetric synthesis of cyclopropanes and aziridines with in situ generation of diazocompounds.

New and useful reactions of chiral sulfur ylides with organoboranes have also been developed and high levels of enantioselectivity have been achieved (Scheme 3).[9]



Scheme 3. Asymmetric synthesis of chiral organoboranes using sulfur ylides.

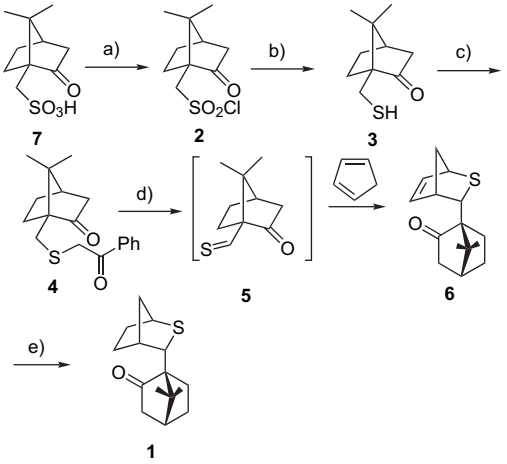
Having developed these useful asymmetric processes, a facile large-scale synthesis of sulfide **1** was sought. Although **1** had been previously prepared in four high yielding steps from camphorsulfonyl chloride (Scheme 4), this process could only be used to prepare **1** on a 5–10 g scale.[10]



Reagents and conditions:
a) PPh_3 (4 equiv.), 1,4-dioxane/H_2O (4:1), reflux, 1 h, 82%.
b) $PhCOCH_2Cl$ (1.1 equiv.), K_2CO_3 (5 equiv.), THF, reflux, 20 h, 82%.
c) cyclopentadiene (20 equiv.), CH_2Cl_2, 20 °C, 16 h, 70%, 20:1 diastereoselectivity.
d) H_2, 1.7% PdS/C, EtOH, r.t., 83%.

Scheme 4. Original protocol for the synthesis of chiral sulfide **1**.[10]

This is a consequence of limitations that arose in two of the key steps: the reduction of camphorsulfonyl chloride, which was limited by the large quantities of triphenylphosphine oxide by-product that must be removed and the photolysis-Diels–Alder reaction, which was limited by the power output of the lamp used. Each step, and in particular these two, was therefore studied in order to find the optimal conditions, with specific attention directed towards finding reaction conditions that could be performed easily on a large scale. The final optimised route is shown in Scheme 5 and is discussed in detail below.



Reagents and conditions:
a) PCl_5 (1.4 equiv.), 4 h, 0 °C ⟶ r.t., 96%.
b) PBu_3 (3 equiv.), 1,4-dioxane/H_2O (4:1), reflux, 15 h, 98%.
c) $PhCOCH_2Cl$ (1.0 equiv.), $NaHCO_3$ (2 equiv.), DMF, r.t., 5 h,100%.
d) cyclopentadiene (40 equiv.), CH_2Cl_2, –20 °C, continuous flow reactor.
e) H_2, 3% Pd/C, EtOH, r.t., 18 h, 59% (two steps).

Scheme 5. Improved synthesis of chiral sulfide **1**.

2. Results and discussion

Initially, the synthesis of the sulfide is started from the commercially available (+)-10-camphorsulfonyl chloride. However, this reagent is rather expensive (£196/100 g, Aldrich) and often contained impurities including (+)-10-camphorsulfonic acid **7**, which had to be removed. We therefore considered starting from (+)-10-camphorsulfonic acid (£33.70/100 g, Aldrich). Following the method reported by Vandewalle and co-workers,[11] (+)-10-camphorsulfonic acid **7** was efficiently converted to the corresponding sulfonyl chloride **2** by phosphorous pentachloride at 0 °C under solvent free conditions (Scheme 5). Recrystallisation of the chloride was necessary before continuing to the next step as the impure material gave significantly reduced yields in the next step (70% cf. 90% with pure material).

The next step of the synthesis was the formation of thiol **3** by reduction of camphorsulfonyl chloride with 4 equiv of triphenylphosphine according to the literature protocol.[10,12] While this reaction worked well giving the thiol **3** in good yield, an unappealing aspect of this procedure was the removal of a large quantity of triphenylphosphine oxide, which was often non-trivial. Therefore, an alternative phosphine was sought that resulted in a water-soluble phosphine oxide thus making it easier to remove. Both trimethylphosphine and tri-*n*-butylphosphine met this requirement although tri-*n*-butylphosphine was chosen, not least because

trimethylphosphine is a sternutator. Interestingly, the water solubility of tri-*n*-butylphosphine oxide has been shown to be greater at low temperature and so extraction was performed using ice cold water.[13] Substituting tri-*n*-butylphosphine for triphenylphosphine under identical conditions (note: the solution was degassed before addition of phosphine) gave the thiol in 85% yield after ice-water extraction and column chromatography. Since only 3 equiv of the phosphine are formally required, we tested the reduction under the reduced loading and this reaction proved very efficient (98%). It could be performed on large scale and unlike the use of 4 equiv, required no chromatographic purification. In the alkylation of thiol **3** with α-chloroacetophenone, it was found that the generation of undesired by-products could be minimised by using DMF in place of the previously employed THF. The use of DMF allowed the reaction to proceed smoothly at an ambient temperature over a shorter time scale and ultimately led to an overall cleaner reaction. The use of a weaker base in this alkylation step also allowed the reaction to proceed more smoothly, so the original base K_2CO_3 was replaced by $NaHCO_3$. The efficient alkylation of the thiol was thus achieved using 1 equiv of α-chloroacetophenone, followed by a simple purifying work-up procedure and removal of solvent in vacuo gave material of sufficient purity for the next transformation (Scheme 5).

2.1. Optimisation of batch photochemical reactor process

While there are a variety of methods available for the generation of thioaldehydes,[14] the photochemical generation of thioaldehydes from phenacyl sulfides, as described by Vedejs and co-workers, is the key step in this synthetic sequence. This method involves the irradiation of a solution of phenacyl sulfide using a sun lamp, in the presence of an excess of cyclopentadiene (Scheme 4).[14a] A copper sulfate bath was used to filter out light of wavelengths below 320 nm, which are believed to cause undesirable secondary photochemical reactions, and the reaction temperature was maintained at 20 °C with the aid of a crystostat. The reaction needs to be degassed since oxygen can sequester the radical intermediates[14a] and this was achieved by simply repeating the procedure of putting the cooled solution (−78 °C) under vacuum (about 15 mbar) followed by charging the vessel with nitrogen twice.

Perhaps the biggest obstacle for the scale up of this reaction is the output of the lamp, since this does not change when the amount of material that is to be photolysed is increased. Ordinarily this would simply require increased reaction times to allow sufficient light to enter the system and thus complete the reaction. However, cyclopentadiene slowly dimerises over time and so prolonged reaction times are not acceptable. Therefore the efficiency of the lamp was examined. It was found that the phenacyl sulfide **4** had two peaks in its UV spectrum (ca. 280 nm and 300 nm). The absorption at ca. 280 nm was attributed to the π–π* transition of the carbonyl group on the camphor moiety and the absorption at ca. 300 nm was assigned to the π–π* transition of the carbonyl that was to be excited. However the spectral output of the lamp (Osram Ultra-Vitalux 300 W sun lamp) was discovered to be very broad and quite weak and therefore not well suited to this reaction, as only a small percentage

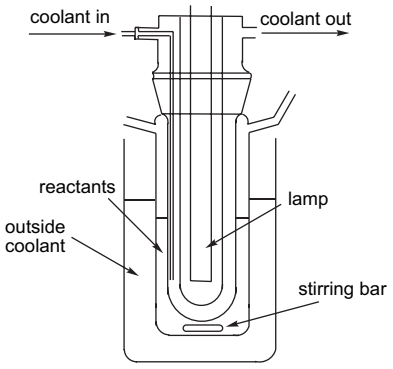


Figure 1. The batch photochemical reactor.

of the relatively weak output was able to excite the molecule into the triplet state. Therefore, a lamp with a higher output in the desired wavelength range was sought. The use of a 125 W mercury arc lamp in a Vycor immersion well provided a suitable alternative (no copper sulfate bath used due to lamp set up—see Fig. 1). Under these conditions the reaction was significantly faster and the product was obtained in similar yield and diastereoselectivity to the original conditions. This allowed 18.2 g of **4** to be processed in a single batch carried out in neat cyclopentadiene (20 equiv). However, the mercury lamp generated a large amount of heat and efficient cooling of the reaction vessel was required to achieve good stereocontrol (Fig. 1). This was carried out by using a circulating coolant on the inner wall and cryostatic cooling to the outer wall, with both set at −10 °C. The reaction was monitored by ^{1}H NMR and it was found that at this temperature good diastereoselectivity (~20:1) was observed. Without internal cooling, the reaction temperature is significantly higher and lower diastereoselectivity (6:1) was obtained, resulting in more difficult downstream problems for separating the diastereomers.

2.2. A single pass, continuous flow photochemical reactor

The use of the batch reactor for this photochemical reaction had certain limitations associated with it that were difficult to overcome and made further scale up inefficient. Most notably, the reaction mixture in the batch reactor is unevenly irradiated. This problem is emphasised when using large volumes of reactant solution, as diffusion in the narrow well is inefficient even with rapid stirring, resulting in reduced yields and increased by-product formation. This problem was overcome by the use of a single pass, continuous flow, Vycor reactor as described by Booker-Milburn and co-workers[15] (Fig. 2).

This consists of three layers of UV transparent tubing (fluorinated ethenepropylene (FEP), 2.7 mm i.d.×3.1 mm o.d.) wound around a traditional cooled immersion well containing a 400 W mercury lamp (Fig. 2b). The reaction solution could then be driven around the reactor through the use of a common HPLC pump (Fig. 2c) and the irradiation time could be defined by the flow rate. This system would then allow large volumes of reaction solution to be processed continuously. The cooling of the reaction solution was efficiently achieved by passing cooled ethylene glycol/water

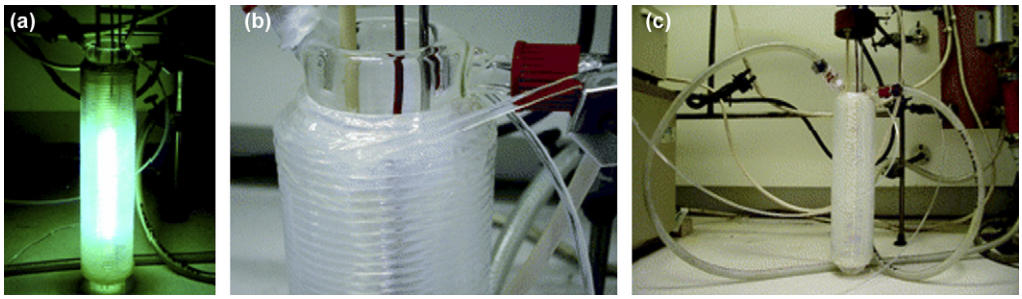


Figure 2. (a) A Vycor/FEP continuous flow chemical reactor. (b) Close-up of FEP tubing (2.7 mm i.d.×3.1 mm o.d.). (c) Attached to water supply and HPLC pump.

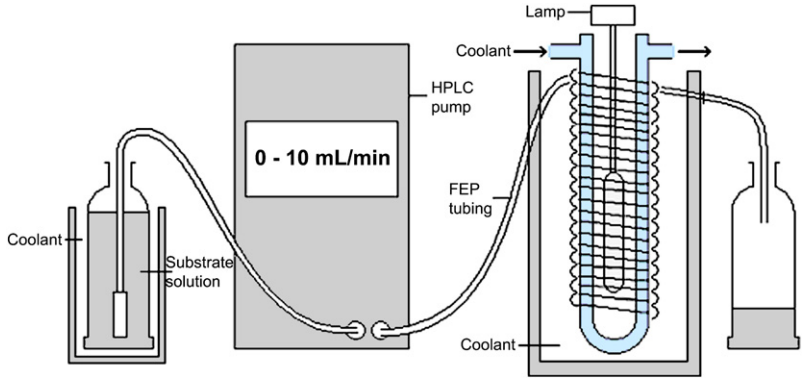
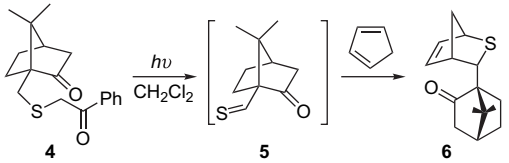


Figure 3. The single pass, continuous flow photochemical reactor.

(1:1) solution at temperature of −5 to −20 °C through the immersion well. In addition to this, the submersion of the entire reactor in an immersion bath of cooled ethylene glycol/water (1:1) solution ensured that the reaction temperature was well maintained. A schematic representation of the continuous flow photochemical reaction is shown in Figure 3.

The optimisation of this process was achieved by exploring how variations in flow rate, acylsulfide concentration, equivalents of cyclopentadiene and temperature affected both the reaction yield and the diastereoselectivity.[16] It was discovered that reducing the sulfide concentration from 0.4 to 0.2 M increased the yield from 43 to 59% (Table 1, entries 1 vs 2). Increasing the equivalents of cyclopentadiene was also shown to have a positive effect on both the yield and diastereoselectivity (Table 1, entries 2 vs 3). Reducing the temperature of the immersion bath from −5 to −20 °C was shown to have a positive effect on the yield, though no change in diastereoselectivity was observed (Table 1, entries 3 vs 4). Finally, a further increase in the amount of cyclopentadiene used (40 equiv) was shown to increase the yield

Table 1. Optimisation of the continuous flow photolysis of sulfide **4**



Entry	Flow rate (ml/min)	Sulfide concn (M)	Cyclopentadiene (equiv)	Internal temp (°C)	External temp (°C)	Yield (%)[a]	d.r.[b]
1	4	0.4	10	−20	−5	43[c]	9:1
2	4	0.2	10	−20	−5	59	10:1
3	4	0.2	20	−20	−5	67	11:1
4	4	0.2	20	−20	−20	72	11:1
5	2[d]	0.2	40	−20	−20	82	11:1
6	2	0.12	40	−20	−20	75	10:1

[a] Yield is calculated by ^{1}H NMR.
[b] Diastereoselectivity is calculated by HPLC using a Discovery® HS C18 568523-U column 25 cm×4.6 mm, 5 μm eluting with a flow rate of 1 mL/min with a gradient of water acetonitrile: 0–25 min from 5 to 95% acetonitrile, 25–27 min 95% acetonitrile, 27–37 min from 95 to 5% acetonitrile, 37–42 min 5% acetonitrile (t_{rminor}: 24.34 min, t_{rmajor}: 24.82 min).
[c] Starting material (25%) was recovered.
[d] A reduced flow rate of 2 mL/min was required as the high viscosity of the solution would not allow the pump to achieve a greater flow rate.

further (Table 1, entries 4 vs 5). A reduced flow rate of 2 mL/min was required when using these conditions due to the high viscosity of the reaction solution, which would not allow the pump system to achieve a greater flow rate. It was considered that on a large scale the problem of viscosity could be circumvented by reducing the concentration of the sulfide in combination with the reduced flow rate, thus giving a more practical set of optimised conditions (Table 1, entry 6). The final large scale (38 g of substrate) optimised conditions for the photolysis of sulfide **4** are shown in Table 1, entry 6 and gave a reaction yield of 75% with a 10:1 d.r.

Throughout this study it proved very difficult to separate the acetophenone by-product from the cycloadduct following the photolysis process, so the crude material was filtered through a short silica plug, and then taken onto the final hydrogenation step. Although initially the pre-poisoned catalyst PdS/C was used, it was found that the reactive double bond could be just as easily reduced using (10%) Pd/C (3 mol % Pd used). Following hydrogenation, the solvent and acetophenone were removed under reduced pressure (30–40 °C, 0.2 mbar), then the residue was passed through a short silica gel pad and the partially purified product recrystallised from pentane, to give the sulfide **1** as a white crystalline solid of >95% d.r.

3. Conclusions

We have developed a practical five-step synthesis of sulfide **1** in 56% overall yield from camphorsulfonic acid. The acid is extremely cheap and readily available in both enantiomeric forms. This practical synthesis of the chiral sulfide not only allows the organocatalytic reaction, which utilises the sulfide to be run on a large scale but also allows the stoichiometric reactions to be run on moderate scale.

4. Experimental

4.1. (+)-10-Camphorsulfonyl chloride (2)[11]

Based on the procedure of Vandewalle and co-workers,[11] (+)-10-Camphorsulfonic acid **7** (100.0 g, 0.43 mol) was placed in a 1 L round-bottomed flask with a gas outlet tube leading to a saturated $NaHCO_3$ trap (as HCl is produced in the reaction). The flask was cooled in a large ice bath and PCl_5 solid (124.0 g, 0.60 mol) was added portion wise. The mixture was agitated manually using a glass rod to initiate the liquefication of the mixture, before being stirred magnetically. After 1 h the cooling bath was removed and the reaction mixture was allowed to warm to rt and stirred for 3 h. The reaction mixture was then slowly poured portion wise into a 2 L separating funnel that was approximately 50% filled with crushed ice. After addition of each portion the separating funnel was thoroughly shaken before further material was added. Once addition of the reaction mixture to the separating funnel was complete, CH_2Cl_2 (500 mL) was added, and the separating funnel was shaken. CH_2Cl_2 layer was removed and the aqueous material was re-extracted with CH_2Cl_2 (2×200 mL). The combined organic fractions were then dried with $MgSO_4$ and the solvent was removed under reduced pressure to afford an off-white crystalline solid. This solid was then recrystallised from petrol to afford the product as white crystalline flakes (104.1 g, 96%). Mp 66–67 °C (hexane) [lit.[17] 67–68 °C (heptane)]; R_f 0.42 (20% EtOAc/petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, s), 1.15 (3H, s), 1.49 (1H, ddd, J=13.0, 9.5 and 4.0 Hz), 1.78 (1H, ddd, J=14.0, 9.5, and 5.0 Hz), 1.99 (1H, d, J=18.5 Hz), 2.05–2.15 (1H, m), 2.17 (1H, $t_{(app.)}$, J=4.5 Hz), 2.40–2.52 (2H, m), 3.73 (1H, d, J=14.5 Hz), 4.31 (1H, d, J=14.5 Hz).

4.2. 7,7-Dimethyl-1-(sulfanylmethyl)bicyclo[2.2.1]-heptan-2-one (3)[10]

4.2.1. Method A: reduction using triphenylphosphine.[10] (+)-(10)-Camphorsulfonyl chloride **2** (14.0 g, 0.06 mmol) and triphenylphosphine (63.3 g, 0.24 mol) were refluxed in a mixture of H_2O (50 mL) and 1,4-dioxane (200 mL) for 1 h. The reaction mixture was allowed to cool to rt and was extracted with petrol (200 mL and 4×100 mL). The combined organic extracts were washed with H_2O (2×100 mL), saturated aqueous NaCl (100 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a yellow oil, which was purified by flash chromatography (3% EtOAc in petrol) to give thiol **3** as a white crystalline solid (9.1 g, 82%). Mp 63–64 °C (EtOAc/petrol) [lit.[18] 65–66 °C]; R_f 0.22 (5% EtOAc/petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, s), 1.02 (3H, s), 1.36–1.43 (1H, m), 1.67–1.75 (1H, m), 1.88–2.04 (4H, m), 2.09 (1H, $t_{(app.)}$, J=5.0 Hz), 2.29–2.42 (2H, m), 2.87 (1H, dd, J=13.5 and 7.0 Hz).

4.2.2. Method B: reduction using tri-*n*-butylphosphine. A solution of (+)-(10)-camphorsulfonyl chloride **2** (50.0 g, 0.2 mol) in 1,4-dioxane (380 mL) was degassed by bubbling N_2 through it for 10 min. Meanwhile, a mixture of H_2O (190 mL) and 1,4-dioxane (380 mL) in a 2 L 3-necked round-bottomed flask fitted with two heat resistant septa, a reflux condenser and a large magnetic stirrer bar was degassed in the same way. After 10 min tri-*n*-butylphosphine (150 mL, 0.6 mol) was added to the H_2O/dioxane mixture via syringe, giving a biphasic solution. This was followed rapidly by the addition of the degassed camphorsulfonyl chloride solution via cannula, which resulted in a monophasic solution. The reaction mixture was then stirred and heated to reflux for 15 h. The reaction mixture was then allowed to cool to rt and transferred to a 5 L separating funnel, where it was partitioned between petrol (1 L) and ice cold H_2O (1 L). The aqueous layer was removed and extracted with petrol (3×500 mL), the total volume of these organic extracts was then reduced to 300 mL and the colourless solution was then washed with ice cold H_2O (3×500 mL) and the solvent evaporated to give a white crystalline solid. The initial petrol layer was washed with ice cold H_2O (3×500 mL) and then evaporated to give a yellow crystalline mass. This was then washed with petrol to give a white crystalline solid. The organic washings were then evaporated to dryness and filtered through a short silica plug (eluent 5% EtOAc in petrol) collecting all fractions that stained a $KMnO_4$ plate. After evaporation of the appropriate fractions, the white crystalline solid obtained was combined with the other solids obtained to give **3** as white crystalline solid (36.0 g, 98%).

4.3. (+)-7,7-Dimethyl-1-{[(2-oxo-2-phenylethyl)-sulfanyl]methyl}bicyclo[2.2.1]heptan-2-one (4)[10]

Using an improved procedure of Vedejs and co-workers,[19] into a solution of **3** (30.0 g, 0.163 mol) and α-chloroacetophenone (1.0 equiv, 25.2 g, 0.163 mol) in DMF (100 mL) was added $NaHCO_3$ (2 equiv, 27.4 g, 0.326 mol). After 5 h the reaction was monitored by either HPLC or ^{1}H NMR to look for complete consumption of the α-chloroacetophenone. If all was consumed the reaction mixture was then diluted with diethyl ether, filtered and washed with diethyl ether. The solution was washed with water (3×100 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford **4** as a pale yellow oil (49.3 g, 100%) that was of sufficient purity to use in the subsequent reaction. If any α-chloroacetophenone remained (lachrymator!), then commercial aqueous ammonia solution (35%, 40 mL) was added and the reaction mixture stirred for 1 h, then cooled in an ice bath and carefully acidified by the portion wise addition of aqueous HCl (1 M). The solution was then diluted with diethyl ether (500 mL) and extracted with aqueous HCl (3×100 mL), water (1×100 mL) and dried over $MgSO_4$. Diethyl ether was removed and the resulting dark orange oil dissolved in ethanol (100 mL) and treated with activated charcoal (5.0 g), then heated to 50 °C for 1 h, allowed to cool, then filtered through Celite and the solvent removed under reduced pressure to afford **4** as a pale yellow oil (49.3 g, 100%) that was of sufficient purity to use in the subsequent reaction. $[\alpha]_D^{21}$ +6.5 (*c* 20, CH_2Cl_2); R_f 0.37 (15% EtOAc in petrol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (3H, s), 1.03 (3H, s), 1.28–1.41 (1H, m), 1.52 (1H, dd, *J*=12.5 and 3.0 Hz), 1.85 (1H, d, *J*=18.0 Hz), 1.90–2.01 (2H, m), 2.06 (1H, $t_{(app.)}$, *J*=4.0 Hz), 2.34 (1H, ddd, *J*=18.0, 4.7 and 2.3 Hz), 2.57 (1H, d, *J*=13.1 Hz), 2.87 (1H, d, *J*=13.1 Hz), 3.87 (2H, s), 7.47 (2H, t, *J*=8.0 Hz), 7.57 (1H, t, *J*=8.0 Hz), 7.98 (2H, d, *J*=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 20.2, 26.8, 26.9, 29.4, 39.6, 43.0, 43.5, 47.8, 61.1, 128.6, 128.7, 133.3, 135.4, 194.6, 217.2.

4.4. General procedure for large-scale photolysis using a batch reactor

The solution of phenacyl sulfide **4** (18.2 g, 60 mmol) and freshly distilled cyclopentadiene (80.0 g, 20 equiv) in a 125 mL Vycor immersion well was cooled in dry ice-acetone. The cooled solution was degassed by repeating the procedure of putting the solution under vacuum (about 15 mbar) followed by charging the vessel with nitrogen twice. The degassed solution was photolysed at −10 °C with a 125 W medium pressure mercury lamp for 9 h (monitored by ^{1}H NMR) *with simultaneous cooling of both the inside and outside walls of the reaction vessel* (Fig. 1). The reaction mixture was then transferred to a round-bottomed flask and the excess cyclopentadiene (51.1 g) was collected under reduced pressure (20 mbar); this could then be recycled if desired. The sulfide was then isolated by passing the crude reaction mixture through a short silica plug (150 g of silica gel), eluting first with petrol to remove the cyclopentadiene dimers until the yellow front line reaches the bottom of the column. The petrol fractions were then discarded and the product and acetophenone were eluted from the silica plug using 2.5% ethyl acetate/petrol, monitoring by TLC (R_f=0.45 [product], 0.43 [acetophenone], 5% ethyl acetate/petrol) to ensure all of the product is collected. The solvent was then removed under reduced pressure to give the partially purified product as a pale yellow oil (65% yield by ^{1}H NMR, using the stoichiometrically produced acetophenone as an internal standard, and 20:1 d.r.), which was dissolved in EtOH (~40 mL) and 10% Pd/C (3.0% based on the Diels–Alder product) was added. The mixture was stirred under a hydrogen atmosphere (7.0 bar) for 18 h (monitored by ^{1}H NMR) and the Pd/C was removed by filtration through a Celite® pad. The solvent and acetophenone (the by-product of the photolysis) were removed under vacuum (30–40 °C, 0.2 mbar), then the residue was passed through a short silica gel pad eluting with 2% ethyl acetate/petrol, to remove the coloured impurities. The crude product was then recrystallised from pentane to afford the sulfide **1** as a white solid (8.21 g, 54%, >95% d.r.). Mp 60–62 °C (MeOH) [lit.[10] 60–62 °C (MeOH)]; $[\alpha]_D^{25}$ +35.9 (*c* 19.5, CH_2Cl_2) [lit.[10] $[\alpha]_D^{25}$ +39.3 (*c* 1.0, MeOH)]; R_f 0.36 (4% EtOAc in petrol); IR ($CDCl_3$) 3025, 2950, 1760, 1230 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, s), 0.96 (3H, s), 1.32–2.08 (11H, m), 2.38 (1H, ddd, *J*=18.2, 4.8 and 3.1 Hz), 2.52–2.66 (1H, m), 3.24–3.32 (1H, br), 3.60 (1H, m), 3.64–3.71 (1H, m); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.6, 21.4, 23.5, 24.4, 27.6, 35.2, 41.3, 42.4, 44.0, 44.7, 45.0, 49.3, 49.9, 62.6, 217.6; MS (EI): *m/z* (%): 250 (85) [M^+], 209 (52), 194 (49) 181 (100); HRMS (EI) (*m/z*) calculated for $C_{15}H_{22}SO$ 250.1391, found 250.1401.

4.5. General procedure for large-scale photolysis using a continuous flow reactor

To a solution of ketosulfide **4** (38 g, 0.126 mol) in CH_2Cl_2 (630 mL) at −20 °C was added freshly distilled cyclopentadiene (420 mL, 5.04 mol) and the reaction mixture degassed for 10 min by the passing of N_2 through the solution. The continuous flow reactor (Fig. 3) was set with the internal and the external cooling systems at −20 °C (ethylene glycol/water 1:1). The 400 W mercury lamp was switched on and degassed CH_2Cl_2 (20 mL) was pumped through the Vycor, three-layer continuous flow reactor at a flow rate of 2 mL/min. The reaction mixture was then pumped through the reactor at a flow rate of 2 mL/min, with collection of the product in a large conical flask. Once the whole solution had passed through the reactor, the tubing was washed with CH_2Cl_2 (350 mL) using the same flow rate. The reaction solution and tube wash were then combined and transferred to a round-bottomed flask and the solvent and cyclopentadiene were removed under reduced pressure (20 mbar). The sulfide was then isolated by passing the crude reaction mixture through a short silica plug (250 g of silica gel), eluting first with petrol to remove the cyclopentadiene dimers until the yellow front line reaches the bottom of the column. The petrol fractions were then discarded and the product was eluted from the silica plug using 2.5% ethyl acetate/petrol, monitoring by TLC (R_f = 0.45 [product], 0.43 [acetophenone], 5% ethyl acetate/petrol) to ensure all of the product is collected. The solvent was then removed under reduced pressure to give the partially purified product as a pale yellow oil (75% yield by ^{1}H NMR, using the stoichiometrically produced acetophenone as an internal standard, and 10:1 d.r. by HPLC), which was dissolved in EtOH (~80 mL) and 10% Pd/C (2.6 g, 2.0 mol % based on sulfide

4 and 3.0% based on the Diels–Alder product) was added. The mixture was stirred under a hydrogen atmosphere (7.0 bar) for 18 h (monitored by ^{1}H NMR) and the Pd/C was removed by filtration through a Celite® pad. The solvent and acetophenone (the by-product of the photolysis) were removed under vacuum (30–40 °C, 0.2 mbar), then the residue was passed through a short silica gel pad eluting with 2% ethyl acetate/petrol to remove the coloured impurities. The crude product was then recrystallised from pentane to afford the sulfide **1** as white solid (18.6 g, 59%, >95% d.r.).

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References and notes

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16. This study was carried out on medium scale (~1.5 g of sulfide per reaction) due to constraints on the availability of starting material. Table 1, entries 1–5 represent medium scale trial reactions. Table 1, entry 6 represent the conditions and results for the 38 g, large scale reaction.
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