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Note

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β-Cyclodextrin-mediated enantioselective photochemical electrocyclization of 1,3-dihydro-2*H*-azepin-2-one

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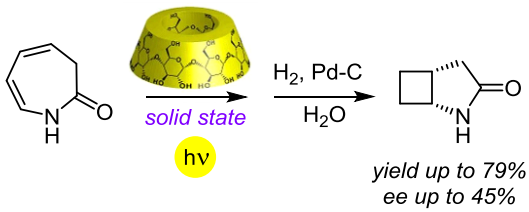
TOC graphic & Abstract



The photochemical electrocyclization reaction of the title compound in the presence of β-cyclodextrin was examined in different conditions. No enantioselectivity was observed in solution, but solid-state reactions of a 1:1 complex as a suspension or a thin film, followed by reduction, provided (1*R*,5*R*)-2-azabicyclo[3.2.0]heptan-3-one in isolated yields up to 79% and with ee values up to 45%.

The importance of light-induced chemistry has long been appreciated and among currently available and sustainable methodologies, organic photochemistry represents a powerful tool for synthetic chemists.[1] Photochirogenesis is an area of major interest,[2] with a significant focus on the use of chiral supramolecular hosts.[3] The cyclodextrins (CDs), water-soluble cyclic oligosaccharides with a truncated cone shape,[4] have been amongst the most widely employed and can facilitate highly selective reactions.[5] While γ-CD is a privileged host for photodimerizations or other bimolecular reactions, the β-CD cavity is better suited for unimolecular transformations of small substrates. To date, two photochemical electrocyclization reactions in the presence of β-CD have been described, implicating *N*-alkylpyridones[6] and tropolone alkyl ethers[7] (Figure 1). In each case, solution-state reactions gave the main photoproduct with negligible enantiomeric excess (ee), whereas solid-state reactions proceeded with around 60% ee in the former case and 25% ee in the latter. Curiously, the absolute configuration of the major enantiomer was not established in either case.

In our own work on the photochemical preparation of functionalized four-membered ring compounds,[8] we recently considered the photochemical electrocyclization reaction of 1,3-dihydro-2*H*-azepin-2-one (**1**).[9,10] The transformation proceeded in ether solution in high yield to give the racemate which was subsequently resolved. We felt that the investigation of an alternative approach to enantiomerically enriched material was warranted, and here we examine β-CD as a chiral host for the photochemical process (Figure 1). The photochemical 4π electrocyclization proceeds in a disroratory fashion leading to a *cis* ring junction; in the asymmetric environment of the β-CD cavity this might lead to a non-racemic product.

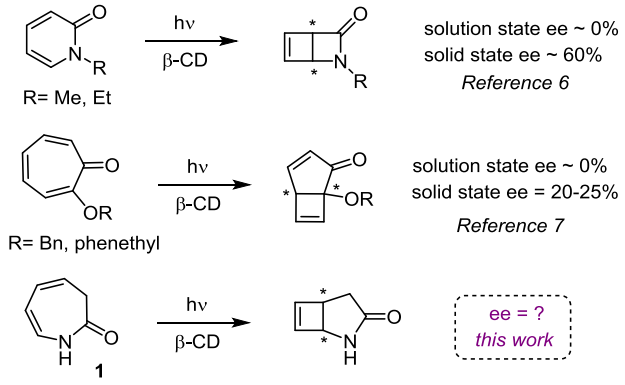
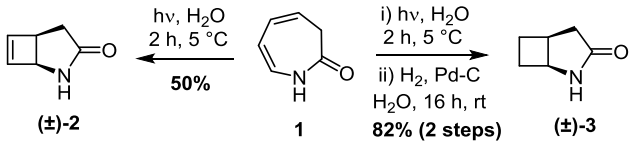


Figure 1. Photochemical electrocyclization reactions performed in the presence of β-CD.

We began by evaluating the photochemical electrocyclization of azepinone **1** in water. An aqueous solution of **1** (15 mM) was placed in a quartz tube and irradiated (λ = 254 nm) for 2 hours. This gave clean and efficient conversion into racemic **2**, which was isolated in 50% yield after lyophilisation (Scheme 1). The conversion was probably higher, but some loss of material was noted during the removal of water;[11] even so, the otherwise clean ^{1}H NMR spectrum of **2** showed some residual water content, testifying to the hydrophilicity of this product.



Scheme 1

With preparative work in mind, we had chosen the concentration in the above control reaction to be close to the aqueous solubility limit of β-CD at room temperature (16.3 mM).[12] However, when 1 equivalent of azepinone **1** was added to a 15 mM aqueous solution of β-CD, a milky white suspension formed. This suspension became a clear solution upon heating to 45 °C, and reappeared upon cooling. We carried out some spectroscopic studies to investigate the solution-state behavior. A ^{1}H NMR titration experiment was performed at 40 °C, whereby incremental amounts of **1** were added to a solution of β-CD (15 mM in D_2O) and the evolution of the ^{1}H chemical shifts was monitored (see ESI). While the signals for protons H_1, H_2, H_4 and H_6 - located on the outside of the β-CD cavity - showed no significant change, protons H_3 and H_5 - located on the inside of the cavity - showed an up-field shift, reaching Δδ values of (respectively) 0.03 and 0.07 ppm at a **1**:β-CD ratio of 1:1. This suggested the presence of a deep-penetration inclusion complex.[13] The titration data for H_3 of β-CD were used to evaluate the binding constant using a recent adaptation of the Benesi–Hildebrand equation;[14a] the value of K_b was estimated to be 35.4 M^{-1}. Complex formation was also supported by a ROESY NMR experiment, again conducted on an equimolar **1**/β-CD mixture in solution at 40 °C (15 mM, D_2O), which displayed intermolecular cross-peaks in the uncongested part of the spectral plot, implicating the unsaturated moiety of the azepinone and the internal β-CD protons H_3 and H_5 (Figure 2).

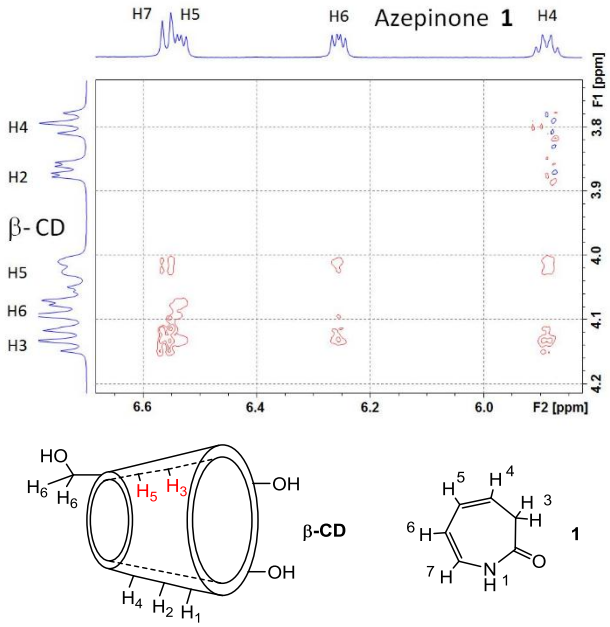


Figure 2. Expansion of part of the 600 MHz solution-state ROESY NMR spectrum of a 1:1 **1**/β-CD mixture (15 mM in D_2O, 40 °C) showing pertinent intermolecular cross-peaks (above). Cartoon of β-CD and structure of **1** showing proton locations (below).

The stoichiometry of the complex was assessed by UV spectroscopy using the continuous variation method.[5e,5i,14] A Job plot of the change in absorption at 254 nm for aqueous solutions of varied relative molar composition suggested complex formation in a 1:1 molar ratio (Figure 3).[15]

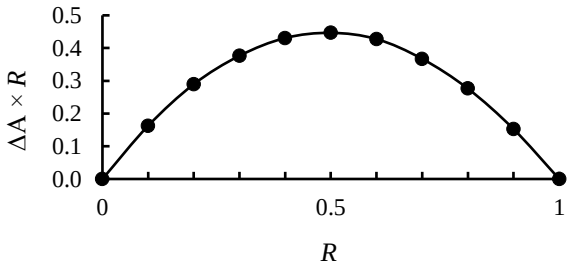


Figure 3. Job plot of UV absorption (λ = 254 nm) at different **1**:β-CD molar ratios.

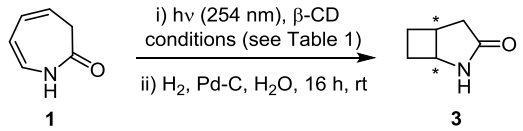
We then began studies of the chiral host–guest photochemical electrocyclization reaction of azepinone **1** in the presence of β-CD in water. However, preliminary efforts were thwarted by extraction problems. While ^{1}H NMR analysis of irradiated reaction mixtures suggested that complete conversion of **1** had been achieved, extensive efforts to isolate the highly water-

soluble bicyclic cyclobutene lactam **2** (liquid–liquid extraction; lyophilisation followed by solid–liquid extraction) provided only small amounts of material.[16] Previously, we had noted that the cyclobutane lactam **3** was more soluble than **2** in organic solvents.[10] We therefore decided to adapt our strategy and transform photoproduct **2** into **3** prior to extraction. In order to verify that this two-step procedure could indeed be carried out, an aqueous solution of **1** (15 mM) was placed in a quartz tube and the solution was irradiated (λ = 254 nm) for 2 hours, as before. The transparent solution was then stirred overnight under an atmosphere of dihydrogen in the presence of 10% Pd-C. After removal of the catalyst the aqueous solution was extracted with ethyl acetate. Pleasingly, the organic extracts provided spectroscopically clean racemic lactam **3** in 82% yield for 2 steps (Scheme 1).

All photochemical studies involving β-CD were therefore carried out using the sequential electrocyclization–reduction protocol as the standard procedure (Table 1). The first experiment was carried out on the clear equimolar **1**/β-CD solution (15 mM) at 45 °C. After 2 hours irradiation the yellow-colored solution was cooled – at which point no precipitation was observed – and reduced to give **3** in 40% yield and with an ee of zero (entry 1). It was suspected that the modest yield was due to thermal degradation during the irradiation, so the second solution-state experiment was conducted at 20 °C. At this temperature, a lower concentration (4 mM) of each component was necessary in order to obtain a clear solution (entry 2). While the isolated yield of **3** (65%) was improved, the ee of the sample remained nil.

We therefore turned our attention to the milky white suspension formed at higher concentration. A suspension was prepared from an equimolar **1**/β-CD solution (each 15 mM), allowing 2 hours stirring to complete the process. Following the standard procedure, the suspension was irradiated at 5 °C then reduced to provide lactam **3** in 79% yield and with a gratifying ee of 38% (Table 1, entry 3). When this experiment was repeated with a two-fold excess of β-CD, the yield remained similar (75%) while the ee rose marginally to 45% (entry 4).[17]

Table 1. Sequential photochemical electrocyclization–reduction of azepinone 1 in the presence of β-CD.



Entry	Irradiation conditions[a]	Sample state[b]	Yield **3** (%)	ee **3** (%)
1	*A*, 45 °C, 2 h	solution	40	0
2	*A*, 20 °C, 2 h	solution[c]	65	0
3	*A*, 5 °C, 2 h	suspension	79	38
4	*A*, 5 °C, 2 h	suspension[d]	75	45
5	*B*, 25 °C, 7 h	powder[e]	70	0-40[f]
6	*B*, 25 °C, 20 h	powder	71	36
7	*C*, 25 °C, 5 h	film	77	41
8	*C*, 25 °C, 5 h	film[g]	77	42
9	*C*, 25 °C, 5 h	film[c]	78	41

a: for details of conditions *A*, *B* and *C*, see experimental section; *b*: all samples were prepared from 15 mM aqueous mixtures of **1** and β-CD (1:1 ratio), except when otherwise indicated; *c*: concentrations of both **1** and β-CD were 4 mM (1:1 ratio); *d*: additional solid β-CD (2 equivalents) was added to the mixture; *e*: solid reagents were mixed directly, no solvent used; *f*: for three identical experiments, the ee values were 0%, 29% and 40%; *g*: concentration of **1** was 7.5 mM (1:2 ratio).

This prompted us to further examine solid-state conditions. Equimolar quantities of **1** and β-CD were ground manually in a mortar and the fine powder placed in a quartz tube and irradiated while the tube was rotated slowly. After 7 hours the irradiation was stopped, since inspection of a small reaction sample by ^{1}H NMR showed no sign of remaining **1**. The powder was dissolved in water and reduced as before, to provide **3** in around 70% yield. This experiment was performed thrice, and for each run the ee value was different: 0%, 29% and 40% (Table 1, entry 5). These results suggested that the grinding process did not give a reproducibly homogeneous sample mixture. Furthermore, variable amounts of caprolactam, the reduction product of non-electrocyclized **1**, were detected: 14%, 0% and 8% in the three experiments, respectively, again was the apparent result of sample heterogeneity. In an effort to ameliorate this, a sample of the white solid obtained from a 15 mM **1**/β-CD aqueous suspension (1:1 ratio) was air-dried and ground finely in a mortar. The powder was irradiated for a longer period (20 h) then reduced as described above to furnish **3** in 71% yield and 36% ee (entry 6) in addition to caprolactam by-product (7%). In these powder-state experiments, the tube rotation resulted in the aggregation of the powder into small “snowballs” that had to be crushed regularly for the electrocyclization to progress.

As an alternative to the powder form of the **1**/β-CD adduct, we investigated thin films. The milky aqueous suspension made from 15 mM **1**/β-CD (1:1 ratio) was spread on a glass plate and left to air-dry to give a smooth film (thickness in the range 20–50 μm). This supported film was irradiated until no starting material **1** remained (5 h) then it was dissolved in water and reduced, as before, to furnish **3** in 77% yield and 41% ee (entry 7). The yield of caprolactam by-product was now <2%. A similar experiment using a film prepared from a 15 mM β-CD solution and 0.5 equivalents of **1** gave almost identical results (entry 8). Finally, a film obtained by slow evaporation of a 4 mM **1**/β-CD aqueous solution (1:1 ratio) was irradiated and reduced in the same way to provide almost identical results (entry 9).

We established the stoichiometry of the solid material implicated in the above reactions. A suspension prepared from a 15 mM equimolar aqueous mixture of **1** and β-CD (as described for entry 3) was filtered and the solid was collected and dried. ^{1}H NMR signal integration of a dilute solution in D_2O indicated a 1:1 ratio. A sample of the same solid was partitioned between ethyl acetate and water; evaporation of these phases gave **1** from the former and β-CD from the latter. Comparison of relative material mass indicated a 1:1 ratio of **1** and β-CD. Interestingly, the same analyses conducted on the suspension obtained from a 1:3 aqueous solution **1**/β-CD mixture (entry 4) also indicated a 1:1 stoichiometry in the solid material.

Although single crystals of the 1:1 complex were not forthcoming, we examined solid samples by scanning electron microscopy (SEM) and powder X-ray diffraction (PXRD) (Figure 4). In the SEM images the **1**/β-CD complex showed a fibrillar morphology in striking contrast with azepinone **1** and β-CD alone, which showed only amorphous block structures. Similarly, the PXRD data obtained for the **1**/β-CD complex were clearly different from those for samples of **1** and β-CD alone. This provided further indication that a genuine complex is implicated, rather than a physical mixture of two discreet substances.

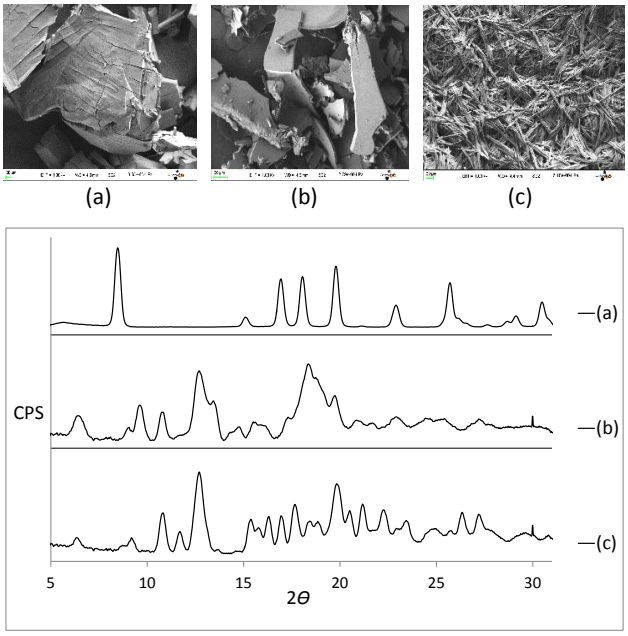
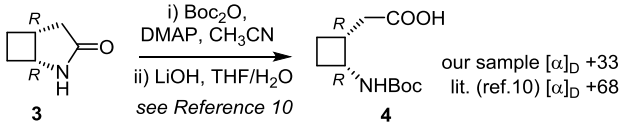


Figure 4. SEM images (above) and PXRD data (below) for: (a) solid **1**; (b) solid β-CD; (c) solid **1**/β-CD complex (from entry 7).

In all the above experiments, HPLC analysis indicated that the same major enantiomer of **3** predominated. To determine its configuration, we transformed a typical sample of **3** (42% ee) into the *N*-Boc-derivative of *cis*-(2-aminocyclobutyl)acetic acid **4** using a known procedure.[10] The sample of **4** thus obtained had $[\alpha]_D^{25}$ +33 (*c* 0.5, $CHCl_3$). The literature value[10] for (*R*,*R*)-**4** (97% ee) is $[\alpha]_D^{27}$ +68 (*c* 0.96, $CHCl_3$), indicating that our samples of **3** have a 1*R*,5*R* absolute configuration (Scheme 2).



Scheme 2.

In summary, the formation of a 1:1 complex between β-CD and 1,3-dihydro-2*H*-azepin-2-one **1** allows the solid-state photochemical electrocyclization of the latter to proceed in good yield in an enantioselective fashion, with ee values up to 45%. This is only the third example of a photochemical electrocyclization reaction conducted in the presence of β-CD, and it confirms and extends the interest and synthetic value of this supramolecular host for photochirogenetic reactions.

Experimental Section

General methods. 1,3-dihydro-2*H*-azepin-2-one **1** was prepared according to the literature.[18] β-CD was obtained commercially (Acros Organics) and was dried (50 °C, 10^{-2} mm Hg) overnight. Ultrapure water (RephiLe PURIST®) was used for all reactions. Analytical grade ethyl acetate was used for all extractions.

Routine NMR spectra were recorded on a Bruker AV360 (360 MHz, for ^{1}H) or a Bruker DPX250 (62.5 MHz, for ^{13}C). Chemical shifts (δ) are reported in ppm with respect to the residual proton signal in deuterated chloroform (δ 7.27 ppm) for ^{1}H and with respect to $CDCl_3$ (δ 77.0 ppm) for ^{13}C. ^{1}H NMR titration experiments were recorded on a Bruker AVII-600 (600 MHz). 2D ROESY spectra (600 MHz) were recorded on the same instrument with a mixing time of 400 ms. The binding constant (K_b) was calculated from the ^{1}H NMR titration experimental data for H3 of β-CD using the Benesi–Hildebrand equation $1/\Delta\delta = 1/(K_b \times \Delta\delta_{sat} \times [\mathbf{1}]) + 1/\Delta\delta_{sat}$, where Δδ is the chemical shift change induced by the presence of **1** at the specified concentration and $\Delta\delta_{sat}$ is the Δδ value at saturation. The linear plot of $1/\Delta\delta$ vs. $1/[\mathbf{1}]$ had a slope of $1/(K_b \times \Delta\delta_{sat})$ and an intercept at $1/\Delta\delta_{sat}$, from which K_b was determined.

UV spectra were recorded on an Analytik-Jena Specord 205 instrument using 1 cm quartz cuvettes. Job plot experiments were performed using 4.0×10^{-4} M solutions of **1** and β-CD in water, mixed to give samples of different molar fraction $R = [\mathbf{1}]/[\mathbf{1}]+[\beta\text{-CD}]$ while maintaining a fixed total concentration. The plot of ($\Delta A \times R$) against R, where ΔA = the difference in absorbance at λ = 254 nm between **1** alone and **1** in the presence of β-CD, gave the R value of the complex stoichiometry.

Enantiomeric excesses (ee) were determined using an Agilent 1260 Infinity HPLC apparatus equipped with a Phenomenex® Lux Cellulose-2 column (250 mm × 4.6 mm; particle size 5 µm) and a UV absorbance (210 nm) detector. Sample solutions were prepared in ethanol (~1 mg mL^{-1}), and the injection volume was 5 µL. Analyses were performed using hexane/EtOH (90/10) as the mobile phase flowing at a rate of 2 mL/min; the column and the mobile phase were thermostated at 20 ± 1 °C. Using these conditions, baseline separation was observed; t_R = 8.1 ± 0.1 min for (1*S*,5*S*)-**3** and t_R = 8.8 ± 0.1 min for (1*R*,5*R*)-**3**. In these same conditions, caprolactam (the reduction product of azepinone **1**) had t_R = 9.8 ± 0.2 min.

Scanning electron microscopy was performed on a Zeiss Supra 55VP instrument equipped with a field emission gun. The sample was deposited on a conductive aluminum sample holder and introduced directly inside the microscope chamber which was then put under a normal secondary high vacuum ($10^{-5}/10^{-6}$ mbar range). The electron beam high voltage was set to 1 kV and the current to a few pA in order to observe the non-conductive products without any conductive deposit on top.

Powder X-ray diffraction data were collected using a Bruker diffractometer equipped with a Micro-focus IμS source and $Cu_{K\alpha}$ radiation. The powders were introduced in 0.3 mm diameter capillaries and measurements were performed in transmission mode at 25 °C. The two-dimensional detector data were integrated into conventional 1D diffraction data using the DIFFRAC.EVA software package V.3.0 (Bruker).

Photochemical reactions. All reactions were carried our using a Rayonet RPR-200 photochemical reactor equipped with a carousel of 254 nm lamps (16 × 6 W). *Conditions A*: the aqueous solution or suspension was magnetically stirred in a vertically-held quartz tube fitted with an internal heating/cooling finger. *Conditions B*: the solid sample was placed in a horizontally-held quartz tube which was rotated mechanically (10 rpm); following the irradiation time, the solid was dissolved in water. *Conditions C*: the thin film was placed on a horizontally held tray located inside the reactor cavity; following irradiation for the specified time using 10 lamps, the solid was dissolved in water.

General procedure for reduction. To an aqueous solution of **2** (also containing β-CD in many cases) obtained from the photochemical reaction was added 10% Pd-C (5 mg). The mixture was stirred under an atmosphere of H_2 (1 atm) for 16 h at room temperature then filtered through a 0.45 μm PVDF syringe filter. The filtrate was extracted with ethyl acetate (10 × 25 mL). Combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give **3**. Sample purity was checked by ^{1}H NMR and HPLC analysis.

Photochemical electrocyclization of 1 in water: *cis*-2-azabicyclo[3.2.0]hept-6-en-3-one 2. A solution of azepinone **1** (50 mg, 0.46 mmol) in water (30 mL) was irradiated for 2 h at 5 °C using *Conditions A*. The reaction medium was lyophilized to give **2** (25 mg, 50%) as a yellow solid, mp 75-78 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.29 (dd, *J* = 17.9 Hz, *J* = 2.9 Hz, 1H), 2.48 (dd,

J = 17.9 Hz, *J* = 10.2 Hz, 1H), 3.54-3.59 (m, 1H), 4.43-4.44 (m, 1H), 6.30-6.38 (m, 2H), 6.46 (br s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 33.6, 41.5, 57.6, 142.2, 142.7, 178.3. These data are in full accordance with those described previously for a sample of **2** obtained by irradiation of **1** in ether.[10]

Sequential photochemical electrocyclization–reduction of 1 in water: *cis*-2-azabicyclo[3.2.0]heptan-3-one 3. A solution of azepinone **1** (50 mg, 0.46 mmol) in water (30 mL) was irradiated for 2 h at 5 °C using *Conditions A*. The reaction mixture was then subjected directly to the *General procedure for reduction* to give **3** (42 mg, 82%) as a yellow oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.86-1.96 (m, 2H), 2.21 (d, *J* = 17.5 Hz, 1H), 2.26-2.36 (m, 2H), 2.50 (dd, *J* = 8.8 Hz, *J* = 17.5 Hz, 1H), 3.06-3.20 (m, 1H), 4.04-4.13 (m, 1H), 6.53 (br s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 25.5, 28.6, 33.3, 37.7, 54.1, 179.0. These data are in full accordance with those described previously for a sample of **3** obtained by hydrogenation of **2** in ethyl acetate.[10]

Sample preparation. Entry numbers refer to Table 1.

Entry 1. A solution of **1** (50 mg, 0.46 mmol) in water (1 mL) was added to a solution of β-CD (520 mg, 0.46 mmol) in water (30 mL). The mixture was heated at 45 °C to ensure it remained a clear solution.

Entry 2. A solution of **1** (50 mg, 0.46 mmol) in water (1 mL) was added to solution of β-CD (520 mg, 0.46 mmol) in water (109 mL).

Entry 3. A solution of **1** (30 mg, 0.28 mmol) in water (1 mL) was added to a solution of β-CD (320 mg, 0.28 mmol) in water (18 mL). Formation of a white precipitate began almost immediately and progressed as the mixture was stirred for 2 h at rt.

Entry 4. As for entry 3, except that further solid β-CD (640 mg, 0.56 mmol) was added when the suspension began to form.

Entry 5. Solid **1** (30 mg, 0.28 mmol) and solid β-CD (320 mg, 0.28 mmol) were ground in a mortar until a fine powder was obtained.

Entry 6. A solution of **1** (50 mg, 0.46 mmol) in water (1 mL) was added to a solution of β-CD (520 mg, 0.46 mmol) in water (30 mL). The white precipitate obtained after stirring for 2 h at rt was filtered through a sintered glass funnel (porosity 3) and washed with water (10 mL). The solid was collected, air-dried, then crushed to a fine powder in a mortar.

Entry 7. A solution of **1** (30 mg, 0.28 mmol) in water (1 mL) was added to a solution of β-CD (320 mg, 0.28 mmol) in water (18 mL). Formation of a white precipitate progressed as the mixture was stirred for 2 h at rt. The milky suspension was spread on a glass plate and left to evaporate and dry in air over 3 days.

Entry 8. As for entry 7, using a solution of **1** (34 mg, 0.31 mmol) in water (1 mL) and a solution of β-CD (702 mg, 0.62 mmol) in water (40 mL).

Entry 9. A solution of **1** (30 mg, 0.28 mmol) in water (1 mL) was added to a solution of β-CD (320 mg, 0.28 mmol) in water (54 mL). The clear solution was spread on a glass plate and left to evaporate and dry in air over 3 days.

Associated content

Supporting Information

Copies of NMR spectra and HPLC chromatograms are presented in the Electronic Supporting Information. The ESI is available free of charge on the ACS Publications website at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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