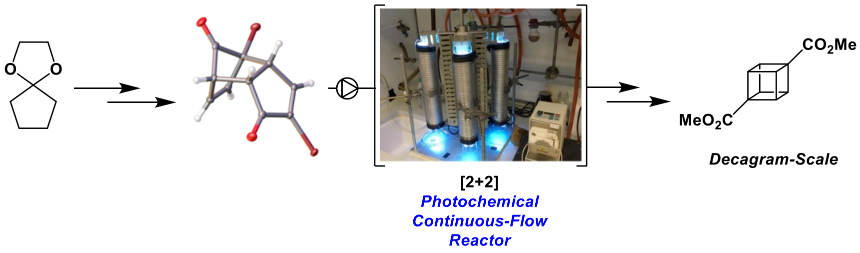
Decagram Synthesis of Dimethyl Cubane Dicarboxylate using Continuous–Flow Photochemistry

Diego E. Collin
Edward H. Jackman
Nicolas Jouandon
Wei Sun
Mark E. Light
D. C. Harrowven
Bruno Linclau*

Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, United Kingdom.

bruno.linclau@soton.ac.uk



Received:
Accepted:
Published online:
DOI:

Abstract The highly strained cubane system is of great interest as a scaffold and rigid linker in both pharmaceutical and materials chemistry. A straightforward approach is reported for the scale–up of a [2+2] photocycloaddition step using convenient home–made flow photoreactors to access dimethyl 1,4–cubanedicarboxylate on decagram–scale in 33 – 40% over 8 steps. The process is demonstrated on 3.4 g.h^{-1} input with 30 minutes residence time, enabling to reduce the process time and to avoid the use of batch photoreactors. Completion of the characterisation of the photocycloadduct and its hydrates is reported.

Key words Cubanes, continuous–flow, photochemistry, photocycloaddition, upscaling

Introduction

The synthesis of dimethyl 1,4–cubanedicarboxylate **1** (Figure 1a) was reported for the first time in 1964 by P. Eaton and T. Cole.[1] The first cubane applications were mainly in the field of energetic materials. Due to its high density (1.29 g cm^{-3}) and bond strain, nitrocubane derivatives have been investigated as non–nuclear explosives (i.e. octanitrocubane, Figure 1b) or propellants.[2,3] However, their complex syntheses make them impractical for such applications. Recently, cubane and cubane dicarboxylic acid have been used in the synthesis of carbon nanothreads and metallic organic frameworks.[4,5] In addition, 1,4–disubstituted cubanes have found interest as non–aromatic rigid spacers in organic materials and polymers.[6-8] Recently, cubanes have been the subject of much interest in medicinal chemistry. Already recognised by Eaton in the 1990s as a potential "3D phenyl bioisostere",[3] it is through the later proposed concept "*Escape from Flatland*",[9] that pharmaceutical research focused on the replacement of benzene rings with 3D saturated isosteres to modulate pharmacokinetics properties (ADME),[10,11] resulting in an increasing demand for access to cubane building blocks.[12-14] The isosteric relationship is based on the cubane diagonal (2.72 Å) being close to that of benzene (2.79 Å) (Figure 1c). Key examples of the study of cubane analogues of drug and agrochemical molecules include diflucuburon, the cubane analogue of diflubenzuron used as insecticidal (Figure 1c) by Tsanaktsidis, Savage, Williams *et al*., and imatinib, by Nicolaou, Vourloumis, Stepan *et al.*, which showed the highest inhibitory activity against the desired target and the greatest cytotoxicity values against cancer cell lines, compared to other saturated cycloalkyl derivatives (Figure 1c).[10,15,16] Polycyclic cage structures such as adamantane, trishomocubane, carborane and cubane have found interest in neurodegenerative diseases due to their hydrophobicity which facilitates transport across the blood–brain barrier in central nervous system.[17,18] Kassiou *et al.* reported antidepressant activity of hydrocarbon–caged compounds, including cubane, in P2X7 antagonists (Figure 1c).[19]

Although different pathways have been reported to construct the cubane cage, cubane functionalisation typically relies on dimethyl 1,4–cubanedicarboxylate as a starting material, (Figure 1a), essentially obtained according to Eaton and Cole's improved synthetic pathway.

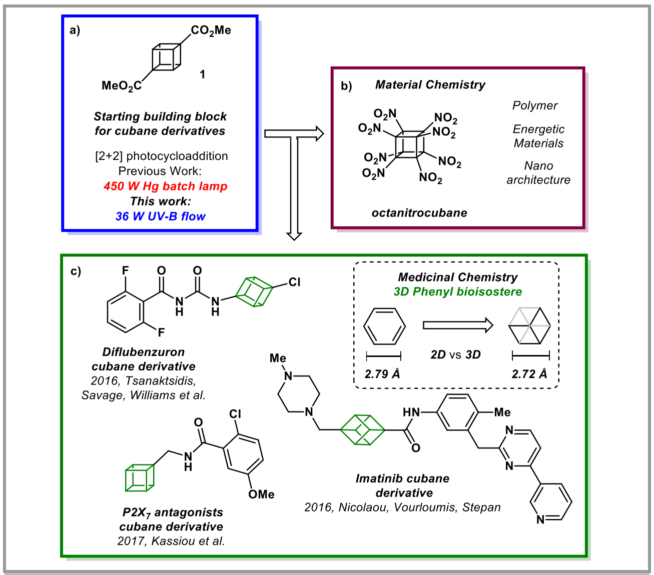
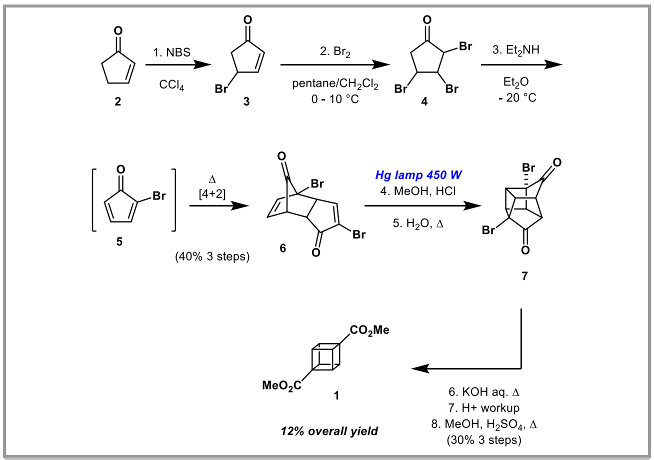


Figure 1 Dimethyl 1,4–cubanedicarboxylate **1** as starting block for cubane derivatives synthesis in medicinal and material chemistry.

The first synthesis of **1** involved 8 steps (Scheme 1),[1] starting with a 2–step tribromination of cyclopentenone **2** using *N*–bromosuccinimide (NBS) and molecular bromine. The tribromocyclopentanone **4** was subjected to a double dehydrobromination to give 2–bromocyclopentadienone **5**, that spontaneously dimerised to give **6**. This [4+2] Diels–Alder cycloaddition occurs with complete regio– and *endo*–selectivity. Afterwards, irradiation of **6** in acidic methanol using a 450 W mercury lamp leads to the formation of the caged intermediate **7**, likely as a mixture of hemiketals. Afterwards, the diketone **7** was obtained *via* deketalisation in refluxing acidic water followed by dessication. Finally, a double Favorskii type rearrangement with acidic workup followed by esterification led to dimethyl 1,4–cubanedicarboxylate (**1**) in 12% overall yield starting from **2**. The scale was not reported by Eaton and Cole in those communications.

Several years later, in 1970, Chapman and co–workers reported several modifications from the original work (Scheme 2).[20] It builds in part upon the work of both Eaton and DePuy on cyclopentadienone ketals,[21] leading to the use of cyclopentanone ethylene ketal **9** as the starting material, instead of **2**.[21] This procedure eliminated the need to use the highly toxic carbon tetrachloride, and the required 1–bromo–1,4–diene moiety was now obtained in one operation, rather than by two successive brominations. In addition, the use of ethylene ketal protection of 2–bromocyclopentadienone (**11** compared to **5**) increased the reactivity for the Diels–Alder dimerization, and the corresponding cycloadduct **12** was obtained in 76% yield from **10**. After selective enone deprotection to give **13**, irradiation with a 450–W Hanovia medium–pressure mercury vapor lamp in benzene of 17 gram (of **13**) for 24 h afforded the caged ketal **14** in 89% yield.

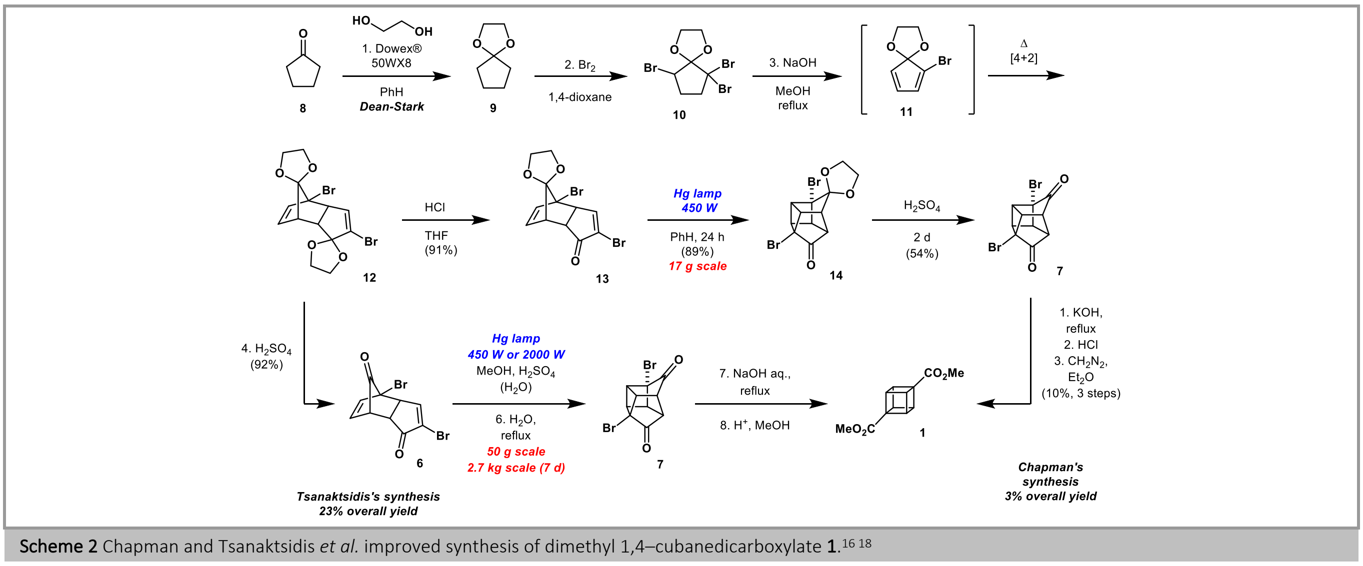


Scheme 1 Eaton and Cole's synthesis of dimethyl 1,4–cubanedicarboxylate **1**.[1]

Subsequently, ketal hydrolysis in harsh acidic conditions gave the caged dione **7** in 43% yield over three steps. Finally, the double Favorskii rearrangement followed by esterification with diazomethane delivered the desired dimethyl 1,4–cubanedicarboxylate **1**. However, problems encountered with that double ring contraction step limited the overall yield to ~3%.

Using key elements from Eaton's and Chapman's approaches, Tsanaktsidis *et al.* reported in 1997 an optimised practical laboratory synthesis of dimethyl 1,4–cubanedicarboxylate **1** on a decagram–scale (Scheme 2).[22] Following Chapman's synthesis of **12**, full deprotection led to Eaton's diketone **6** allowing the photochemical step to be conducted on 50 gram scale with a 450 W mercury lamp in a batch photoreactor, although the irradiation time was not reported.[22] Moreover, Tsanaktsidis and co–workers obtained an improvement of the double ring contraction rearrangement, reporting that higher yields could be obtained when ≤ 12 mL of 25% aqueous NaOH per gram of **7** were used. An overall yield ranging from 42 to 47 % was obtained, from **6** to **1**, in contrast to 30% of Eaton's and Cole.

Furthermore, in 2013, the same group reported a pilot–scale synthesis for the production of half kilogram quantities of **1**. The [2+2] photocycloaddition step was implemented in a custom–build semi–batch flow photoreactor with a 2000 W medium pressure Hg lamp, in which the solution was continuously recirculated through the flow cell at a rate of 4L.min^{-1}, during 7 days (173 h).[23]



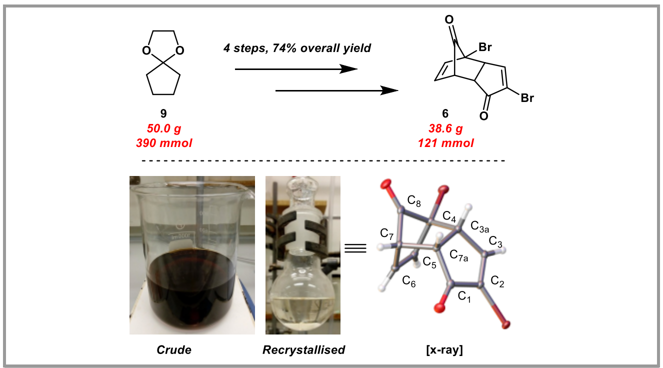
Scheme 2 Chapman and Tsanaktsidis *et al.* improved synthesis of dimethyl 1,4–cubanedicarboxylate **1**.[16 18]

Dimethyl 1,4–cubanedicarboxylate remains an expensive starting material to purchase (≈ £ 400 – 600 for 1 g) and, in addition to the 8–steps required, the [2+2] photocycloaddition step represents a practical barrier for upscaling using batch photoreactors.[24-26] We report here a modification of the process using a home–made microflow photoreactor for achieving the photocycloaddition step on large scale with a throughput of 34 g in 10 h, that is conveniently conducted in a fumehood using inexpensive and easily assembled equipment with a low–powered 36 W lamp.[25-27]

Results and Discussion

Synthesis of the cycloadduct

The cycloadduct **6** was obtained following Tsanaktsidis' procedure.[23] Starting from **9**, dimer **12** was obtained as a beige solid in 89% yield without any chromatographic purification, with acetal hydrolysis next giving *endo*–2,4–dibromodicyclopentadiene–1,8–dione (**6**) in 86% yield by precipitation in an ice–water bath. Interestingly, dissolving the obtained solid in methanol led to a dark solution (Scheme 3), which was consistent with Tsanaktsidis' observations,[19] who reported that it did not impede the [2+2] cycloaddition step in a batch photoreactor.[19] Nevertheless, **6** was subjected to further purification by recrystallisation from hexane/ethyl acetate (2:1)[18] in order to prevent fouling of the flow microreactor, and to assure reproducibility with a fully transparent solution. Notably, these precautions produced colourless crystals that gave a colorless solution upon dissolving in methanol (Scheme 3) and additionally allowed its crystal structure to be recorded. Overall, the recrystallised [4+2] cycloadduct **6** was obtained in 4 steps from cyclopentanone ethylene ketal **9** in 75% yield.



Scheme 3 Synthesis of the cycloadduct **6** *via* Tsanaktsidis's reported procedure.

Structure of the photocycloaddition product

The optimisation of the [2+2] photocycloaddition step using continuous–flow required full characterision of the reaction mixture components. While Eaton and Chapman reported ^1H NMR data of the dione **7**, in our hands, the spectra obtained from evaporating flow reactor output aliquots proved to be much more complex (see Figure S7, Supporting Information). Because the photochemical step was carried out in acidic methanol/water, dione **7** was accompanied by its hydrates **7a** and **7b** (Scheme 4). While this had been noted by Eaton, Chapman and Tsanaktsidis,[1,20,22,23] to the best of our knowledge no characterisation of these species is available. In addition, **7** had only been characterised by ^1H NMR (at 100 MHz), in which the overlapping individual proton environments could not be assigned.[1,20] In order to achieve full mixture analysis of the collected crude samples at the outlet of the reactor, a full characterisation of **7** and its hydrate derivatives was undertaken.

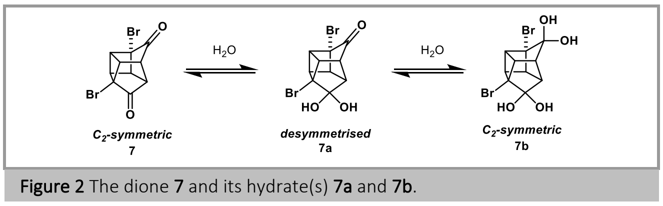


Figure 2 The dione **7** and its hydrate(s) **7a** and **7b**.

The dione **7** could be isolated *via* repeated azeotropic distillation using toluene. In contrast to the hydrate forms **7a** and **7b**, the dione **7** was soluble in chloroform. Upon standing however, the ketone slowly rehydrates if it is not stored over P_2O_5 in a dessicator.

As depicted in Figure 2, **7** possesses a C_2–rotational axis going through the middle of two bonds (indicated in yellow, Figure 3). Therefore, only three chemically distinct proton environments are expected by ^{1}H NMR analysis, with H–3 and H–1 as doublets and H–2 as a doublet of doublets, which, at higher field (400 MHz), could be observed in the ^{1}H NMR spectrum. In addition, the five environments observed in the ^{13}C NMR spectrum clearly indicated two–fold molecular symmetry, with the resonance at 203.2 ppm showing the presence of the carbonyl groups. Full assignment of the spectra was achieved (Table S2, Supporting information), enabling a correction to the reported data for **7** (Table S1, Supporting information).[28]

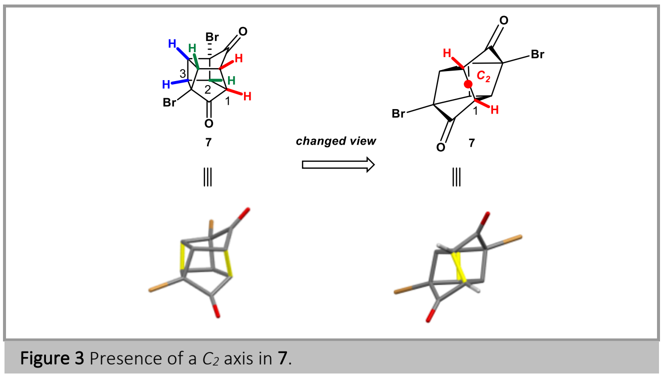


Figure 3 Presence of a C_2 axis in **7**.

The C_2–symmetric dihydrate (**7b**) and the non–symmetric monohydrate (**7a**) (Figure 3) could not be separated. Desymmetrisation of **7** leads to six chemically non–equivalent protons) and a significant increase in the number of proton environments, explaining the more complex ^{1}H NMR spectra obtained (Figure S7, Supporting information). The observation of only one carbonyl peak (205.9 ppm) in the ^{13}C NMR spectrum together with two hydrate carbon peaks (106.1 ppm) and nine C–H (3 + 6) peaks, confirmed the presence of both the mono– and dihydrates (Table S1, Supporting Information). The ^{1}H COSY NMR analysis allowed assignment of the resonances of the dihydrate and of the monohydrate (Figure S8, Supporting Information).

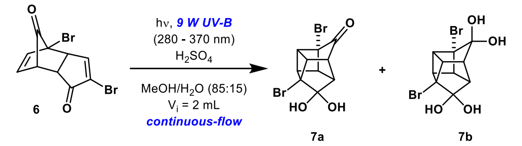
Pleasingly, despite the spectral complexity, those results revealed that only the desired carbocycle was formed during irradiation. Moreover, the conversion towards **7** according to residence time in continuous–flow could be now easily calculated (see Supporting Information section 8).

Intramolecular [2+2] photocycloaddition

The photoreactors used for the [2+2] photocycloaddition were constructed using commercially available parts through scaling our previously reported set–up.[29] Low–power 9 W and 36 W lamps were used. The lamps were fitted in a quartz tube with one layer of FEP tubing (0.8 mm ID x 1.6 mm OD) wrapped around. For the large–scale reactor, the FEP tubing was surrounded with water–cooled tubing, with aluminium foil added between both layers of tubing. A syringe pump was used for preliminary and small–scale experiments otherwise a peristaltic pump was used (Figures S3, S4, Supporting Information).

Our initial efforts started with the irradiation of recrystallised **6** using a 9 W UV–C lamp (λ = 254 nm) (Figure 4a). However, after 1 h, fouling of the tubing was observed (Figure S6), resulting in the presence of a yellow coating on the inner wall of the tubing. Nevertheless, product isolated after irradiation for 8 h gave, after carrying out the Favorskii followed by acidification, 1,4–cubanedicarboxylic acid **15** in 52% yield over the 3 steps from **6** (377 mg scale). The fouling could be avoided by changing the UV–C lamp for a 9 W UV–B broadband lamp (λ = 280 – 370 nm). As observed in Table 1, quantitative conversion of dione **6** was achieved after 45 minutes under photoirradiation (Entry 4, Table 1). Doubling the concentration was tried in order to improve the throughput, (Entry 6 and 7, Table 1), however, no gain was obtained as the residence time had to be increased accordingly to achieve the same conversion (Entry 7, Table 1).

Table 1 Residence time screening for conversion of dione **7a** and **7b** under 9 W UV–B broadband irradiation.

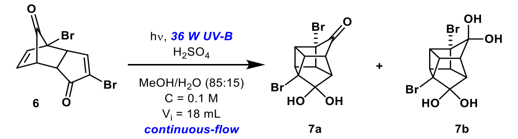


Entry	Concentration [M]	Flow rate [mL.min^{-1}]	Residence time [min]	Conversion [%]
1	0.1	0.400	5	44
2	0.1	0.133	15	74
3	0.1	0.066	30	94
4	**0.1**	**0.044**	**45**	**>99**
5	0.1	0.033	60	>99
6	0.2	0.044	45	66
7	**0.2**	**0.022**	**90**	**>99**

[a] Calculated by ^{1}H NMR (See Supporting information section 8).

Under the optimum conditions, the 2 mL continuous–flow reactor enabled synthesis of **7** on milligram–scale with a theoretical productivity (P_{theo}) of 83 mg.h^{-1}. Next, upscaling of the process was investigated. The 9 W UV–B lamp was switched for 36 W UV–B narrowband and broadband lamps. In our type of setup, the use of a stronger lamp required an increase in the reactor volume. The UV–B narrowband lamp emits from 280 to 315 nm with one major peak at 311 nm whereas the UV–B broadband emits from 280 to 370 nm with a major peak at 302 nm (Figure S2, Supporting Information). As noted in Table 2, these lamps performed equally well with little difference in residence time required to achieve full conversion (entries 3–4 and 7–8) despite the broadband spectrum showing a better overlap with the UV–spectrum of **6** (Figure S5, Supporting Information). For both lamps, quantitative conversion was reached after 30 minutes of passing through the reactor (Entries 3 and 7, Table 2).

Table 2 Residence time screening for conversion of dione **7a** and **7b** under 36 W UV–B broadband and narrowband respectively.



Lamp	Entry	Flow rate [mL.min^{-1}]	Residence time [min]	Conversion [%][a]
UV-B broadband (36 W)	1	3.6	5	14
	2	1.2	15	46
	3	**0.6**	**30**	**>99**
	4	0.4	45	>99
UV-B narrowband (36 W)	5	3.6	5	20
	6	1.2	15	50
	7	**0.6**	**30**	**>99**
	8	0.4	45	>99

[a] Calculated by ^{1}H NMR scale (See Supporting information section 8).

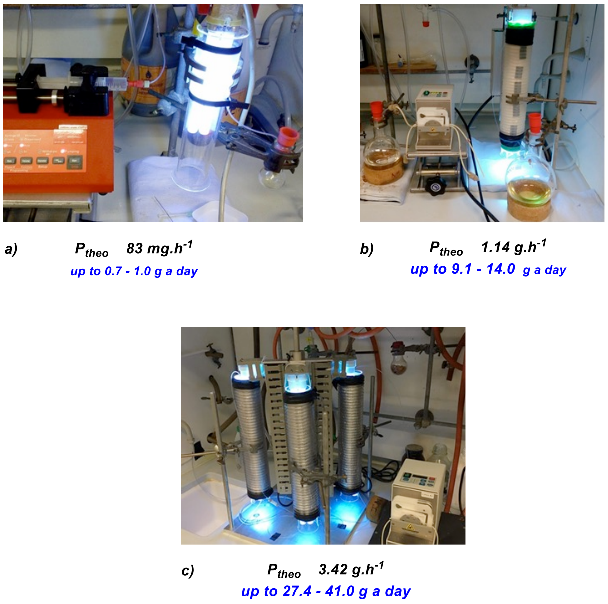
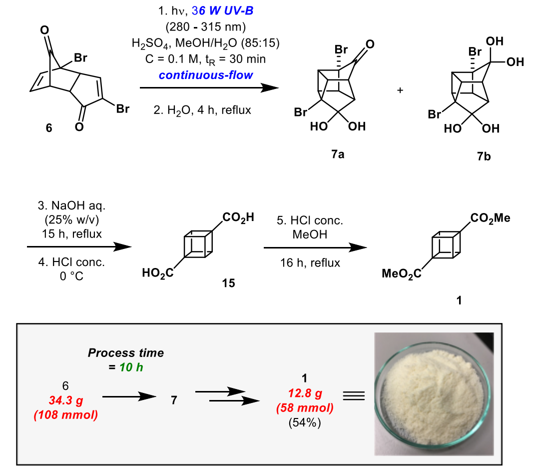


Figure 4 Custom–built reactors pictures and numbering–up strategy to increase the throughput. a) 9 W UV–B broadband and internal volume (V_i) = 2 mL. b) 36 W UV–B narrowband and V_i = 18 mL. c) 3 × 36 W UV–B narrowband and V_i = 54 mL (In blue, up to x–y g a day, x referring to 8h and y referring to 12 h) See Figures S3,S4 for enlarged pictures.

By increasing the internal volume of the reactor 9–fold, and the power of the lamp to 36 W, the theoretical productivity was increased from 83 mg.h^{-1} to 1.14 g.h^{-1} (Figure 4b). To increase the throughput for the decagram–scale of the desired product **1**, we added two similar photoreactors, to increase the internal volume from 18 mL to 54 mL enabling to increase the flow rate while keeping the same residence time as well as the same tube diameter (Figure 4c). The latter is known to be relevant in upscaling photochemical reactions.[26] For commercial availability reasons, the UV–B narrowband lamp was preferred over the broadband lamp.

Subsequent reflux of the product mixture in water ensured complete hydrolysis to **7a** and **7b**. The double ring contraction was then effected using Tsanaktsidis's conditions (Scheme 4), with acidification by cold concentrated hydrochloric acid gaving cubane dicarboxylic acid **1.8**, which we could not obtain in completely pure form.[22,23] Therefore, esterification of the carboxylic acids was carried out. It was found that the use of hydrochloric acid gave the best results on decagram–scale. Purification was achieved by column chromatography enabling the isolation of dimethyl 1,4–cubanedicarboxylate **1** without the need of recrystallisation as previously reported (Scheme 4).[22,23]

Finally, with this 3–coil reactor setup and the optimised conditions, 34.3 g of dione **6** were transformed into **7** after 10 h with quantitative conversion. The following 4 steps sequence, double Favorskii rearrangement, acidification and esterification enabled us to isolate 12.8 g of pure dimethyl 1,4–cubanedicarboxylate **1** in 54% overall yield over 4 steps from **6** (Scheme 4). The complete synthesis has been carried out several times starting on 50–gram scale of the cyclopentanone ethylene ketal **3**, in total yields ranging from 33 – 40%, with the synthesis of the cycloadduct **6** being the yield–determining step.[23]



Scheme 4 [2+2] photocycloaddition (1), double ring contraction (2), acidification (3) and esterification step (4) for synthesis of dimethyl 1,4–cubanedicarboxylate **1**.

Conclusion

In conclusion, unlike the previously reported syntheses, the [2+2] photochemical step has been implemented under a continuous–flow process. The photoreactor has been developed according a "Do–it–yourself" (DIY) approach with inexpensive commercially available equipment enabling a drastic reduction in the process time while removing the need for expensive batch photoreactors. Moreover, unlike the batch photoreactors used previously, the number of reactors used can be adjusted according the processed scale. Careful analysis of the reaction mixture after irradiation allowed full characterisation of the photocycloadduct **7** and its hydrates. Dimethyl 1,4–cubanedicarboxylate **1** was obtained in decagram–scale quantities in overall yields between 33 – 40%. We hope that the demonstration of facile access to this cubane starting building block in reasonable quantity using continuous–flow will find interest in academic research and help to expand the knowledge about less explored 3D moieties such as cubane.

The experimental section has no title; please leave this line here.

General Synthesis Conditions

Solvents and reagents were used as received from standard chemical suppliers unless otherwise stated. Flash column chromatography was performed with Sigma Aldrich 60 silica gel (40–63 micron). Fourier–transform infrared (FT–IR) spectra are reported in wavenumbers (cm^{-1}) and were recorded using a diamond ATR accessory, as solids or neat liquids. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, DMSO–*d*$_6$ and CD_3OD solutions at 298 K at 400 MHz. Chemical shifts are reported in δ units using $CHCl_3$ (δ 7.27 ppm ^{1}H, δ 77.00 ppm ^{13}C), DMSO–*d*$_6$ (δ 2.51 ppm ^{1}H, δ 77.00 ppm ^{13}C) CD_3OD (δ 3.31 ppm ^{1}H, δ 77.00 ppm ^{13}C) as an internal standard. The following abbreviations for the multiplicity of the peaks are s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sxt (sextet), spt (septet), oct (octet) br (broad), and m (multiplet). Melting points were obtained in an open capillary and are uncorrected.

Safety note: cubane dicarboxylic acid is known to be shock–sensitive.[30].

Continuous–Flow Experiments

The microfluidic devices were constructed with Adtech Polymer Engineering® FEP tubing (0.8 mm ID x 1.6 mm OD). The connections were made with Upchurch Scientific® Super Flangeless™ nuts (natural PEEK, ¼–28 Flat-Bottom for 1/16 OD tubing) and Upchurch Scientific® Super Flangeless™ ferrules (yellow ETFE, ¼–28 Flat–Bottom for 1/16 OD tubing). Upchurch Scientific® Luer Adapters (PEEK, 1/4–28 Female to Female) were used to connect syringes to the tubing. The feed solutions were conveyed to the microreactors using an Aladdin Single–Syringe Pump or an Ismatec® REGLO Digital Ms–2/6 peristaltic pump for large–scale reactions. Osram® (UVC 9W G23), Phillips® UVB–Broadand (PL–S 9W/12/2P) and Phillips® UVB–Narrowband (PL–L 36W/01/4P) lamps were used for the different experiments reported.

Procedures

Synthesis of 1,4–dioxaspiro[4.4]nonane (9)

[CAS Reg. No. 176-32-9]

A solution cyclopentanone **8** (100 mL, 1.13 mol, 1.0 equiv.) and ethylene glycol (80 mL, 1.44 mol, 1.3 equiv.) in anhydrous benzene (200 mL) containing Dowex® 50WX8 50–100 (H) cation exchange resin (1.20 g, prewashed with anhydrous MeOH, followed by drying under vacuum) was heated at reflux under a Dean and Stark apparatus for 30 h. After cooling to room temperature, the resulting yellow mixture was washed with NaOH (4%) (2 × 100 mL) and brine (2 × 200 mL), dried over $MgSO_4$ and distilled to afford 1,4–dioxaspiro[4.4]nonane **9** (112.6 g, 0.88 mol, 78%) as a colourless oil.

Formula $C_7H_{12}O_2$

MW 128.17 $g.mol^{-1}$

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.90 (s, 4H), 1.81 – 1.74 (m, 4H), 1.71 – 1.65 (m, 4H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 118.5, 64.2, 35.9 (2C, CH_2), 23.5 (2C, CH_2) ppm.

Data consistent with the literature.[30]

Synthesis of E*ndo*–2,4–dibromodicyclopentadiene–1,8–dione bisethylene ketal (12)

[CAS Reg. No. 2408937-98-2]

A solution of 1,4–dioxaspiro[4.4]nonane **9** (50.0 g, 390.0 mmol, 1.0 equiv.) in anhydrous 1,4–dioxane (310 mL) at 5 – 10 °C was purged with argon over 15 minutes. Molecular bromine (70 mL, 1.37 mol, 3.5 equiv.) was added dropwise (2 h), ensuring that the temperature was maintained between 10 – 15 °C, before being stirred at room temperature for 20 h. A NaOH (4%) trap was linked to the reaction flask to ensure the trapping of formed HBr. A solution of NaOH (121.4 g, 3.04 mol, 7.8 equiv.) in MeOH (610 mL) was added dropwise via a dropping funnel over 2 h then the resulting brown mixture was heated at reflux for 24 h, before being cooled to room temperature and poured into a stirred ice–water bath (1.5 L). After filtration, the beige precipitate was washed with ice–cold H_2O (200 mL) and dried under high–vacuum for 6 h, to afford *endo*–2,4–dibromodicyclopentadiene–1,8–dione bisethylene ketal **12** (69.78 g, 171.8 mmol, 88%) as a pale beige solid.

Formula $C_{14}H_{14}O_4Br_2$;

MW 406.07 g mol^{-1}

mp 180 – 181 °C (hexane/EtOAc)

IR 2986 (w), 2890 (w), 1616 (w), 1471 (w), 1266 (m), 1142 (m), 1008 (s), 954 (s) 743 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.19 (dd, *J* = 6.4, 3.7 Hz, 1H, H_6), 6.08 (d, *J* = 2.3 Hz, 1H, H_3), 5.84 (dd, *J* = 6.5, 0.7 Hz, 1H, H_5), 4.28 – 4.11 (4H, m, acetal), 4.04 – 3.87 (4H, m, acetal), 3.51 (dd, *J* = 7.4, 2.4 Hz, 1H, H_{3a}), 3.08 (1H, dd, J 7.4, 4.7 Hz, H_{7a}), 2.73 (1H, td, *J* = 4.7, 0.7 Hz, H_7) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 134.5 (C_3H), 133.1 (C_5H), 132.6 (C_6H), 128.1 (C_1O), 126.1 (C_8O), 115.9 (C_2Br), 67.8 (C_4Br), 66.4 (acetal), 66.3 (acetal), 65.3 (acetal), 65.2 (acetal), 55.7 ($C_{3a}H$), 49.6 ($C_{7a}H$), 47.3 (C_7H) ppm.

Data consistent with the literature.[22]

Synthesis of *Endo*–2,4–dibromocyclopentadiene–1,8–dione (6)

[CAS Reg. No. 2408937-98-2]

To a 500 mL flask, *endo*–2,4–dibromodicyclopentadiene–1,8–dione bisethylene ketal **12** (58.5 g, 0.144 mol, 1.0 equiv.) was dissolved portionwise in concentrated H_2SO_4 (>95%) (180 mL) at room temperature. After 30 h stirring at room temperature, the solution was slowly poured into a vigorously stirred ice–water bath (1 L), forming a beige precipitate. The resulting slurry was filtered under vacuum, washed with cold H_2O and dried under high–vacuum. The crude solid (47.2 g) was dissolved in EtOAc (472 mL) in a 2 L beaker with heating and stirring, then hexane (236 mL) was added. The pale beige precipitate formed was isolated by vacuum filtration, washed with ice–cold hexane/EtOAc (75 mL, 1:1), dried under vacuum and recrystallised from EtOAc/hexane to yield the title compound (28.15 g, 0.089 mol) as colourless crystals. Further evaporation of the filtrate gave a second crop (10.49 g, 0.033 mol) of colourless crystals to afford, overall, *endo*–2,4–dibromocyclopentadiene–1,8–dione **6** (38.64 g, 121.0 mmol, 84%).

Formula $C_{10}H_6O_2Br_2$

MW 317.96 g mol^{-1}

mp 164 – 165 °C as crystals.

IR 1789 (s), 1717 (s), 1580 (w), 1554 (w), 985 (m), 886 (m), 722 (s), 684 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (d, *J* = 2.9 Hz, 1H, H_3), 6.36 (dd, *J* = 7.0, 3.9 Hz, 1H, H_6), 6.26 (dt, *J* = 6.8, 0.9 Hz, 1H, H_5), 3.59 (ddd, *J* = 4.8, 3.9, 0.9 Hz, 1H, H_7), 3.53 (1H, dd, *J* = 6.5, 2.9 Hz, H_{3a}), 3.21 (1H, dd, *J* = 6.4, 5.1 Hz, H_{7a}) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.0 (C_1O), 192.4 (C_8O), 156.4 (C_3H), 134.1 (C_5H), 133.9 (C_6H), 129.8 (C_2Br), 60.3 (C_4Br), 49.0 ($C_{3a}H$), 47.3 (C_7H), 44.1 ($C_{7a}H$) ppm;

Data consistent with the literature.[22]

Synthesis of Dimethyl 1,4–cubanedicarboxylate (1)

[CAS Reg. No. 2408937-98-2] 1,4–cubanedicarboxylic acid

[CAS Reg. No. 29412-62-2] Dimethyl 1,4–cubanedicarboxylate

In a 2 L flask, *endo*–2,4–dibromocyclopentadiene–1,8–one **6** (34.31 g, 108.0 mmol, 1.0 equiv.) was dissolved in MeOH (907 mL), H_2O (163 mL) and H_2SO_4 (1.36 mL) then degassed with bubbling argon for 15 minutes. The resulting colourless solution was pumped (flow rate of 1.8 mL.min^{-1}) through the photoflow microreactor (V_i = 54 mL) using a peristaltic pump and a 36 W UV–B narrowband lamp. After reaching the steady–state (≈ 50 min), the product stream was collected until the solution had passed through the photoreactor. Pure methanol was then pumped through for 50 minutes. The resulting yellow solution was concentrated under vacuum then the obtained solid was heated at reflux in H_2O (312 mL) for 3.5 h to ensure full hydrolysis of any remaining dimethyl ketal. On cooling to room temperature, aq. NaOH (81.12 g, 26% w/v, 312 mL) was added portionwise to the mixture, and the dark brown solution stirred for 15 h at reflux. The solution was cooled to 0 °C, and concentrated HCl (~ 160 mL) was added dropwise until a pH ≈ 1 – 2 was reached. The brown precipitate was filtrated, and washed successively with ice–cold H_2O (200 mL) and ice–cold MeOH (15 mL). The crude solid was concentrated under high–vacuum for 6 h, then transferred to a 250 mL flask and heated under reduced pressure for several hours (60 °C) to afford 1,4–cubanedicarboxylic acid **15** (≈ 17.93 g) as a brown crude solid.

Afterwards, to 1,4–cubanedicarboxylic acid **15** (7.00 g) in anhydrous MeOH (200 mL) under argon in a 500 mL flask, was added concentrated HCl (2.0 mL, 66.0 mmol, 1.8 equiv.) dropwise. After 16 h at reflux under argon, the solvent was concentrated under vacuum and the obtained solid dissolved in CH_2Cl_2 (150 mL). The organic phase was washed with H_2O (7 × 100 mL), then the aqueous phases were combined and extracted with CH_2Cl_2 (4 × 150 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated under vacuum. The obtained black solid was dry–loaded and purified by flash column chromatography (8:2 hexane/EtOAc) to afford dimethyl 1,4–cubanedicarboxylate **1** (5.67 g, 25.7 mmol) as a white solid. This was subsequently repeated with 1,4–cubanedicarboxylic acid **15** (8.56 g) in anhydrous MeOH (245 mL) and concentrated HCl (2.45 mL, 0.081 mol, 1.8 equiv.), as above, to afford dimethyl 1,4–cubanedicarboxylate **1** (7.12 g, 32.3 mmol). Dimethyl 1,4–cubanedicarboxylate **1** (12.79 g, 58.1 mmol) was thus obtained in 54% overall yield from *endo*–2,4–dibromocyclopentadiene–1,8–one **6.**

1,4–Cubanedicarboxylic acid (15)

Formula $C_{10}H_8O_4$

MW 192.17 g mol^{-1}

^1H NMR (400 MHz, CD_3OD) δ = 4.19 (s, 6H) ppm.

^{13}C NMR (101 MHz, CD_3OD) δ = 175.5 (2C, CO), 57.8 (2C, C cubyl), 48.3 (6C, CH cubyl) ppm.

Data consistent with the literature.[22]

Dimethyl 1,4–cubanedicarboxylate (6)

Formula $C_{12}H_{12}O_4$

MW 220.22 g mol^{-1}

R_f 0.51 (8:2 hexane/EtOAc)

mp 163 – 164 °C

IR 3000 (s), 2955 (w), 1717 (s), 1440 (s), 1323 (s), 1206 (s), 1089 (s) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ = 4.25 (s, 6H), 3.72 (s, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 172.0 (2C, CO), 55.8 (2C, C cubyl), 51.6 (2C, CO_2CH_3), 47.1 (6C, CH cubyl) ppm.

Data consistent with the literature.[22]

Funding Information

The authors acknowledge financial support from the ERDF (LabFact: InterReg V project 121) and EPSRC (Photo-Electro Programme Grant EP/P013341/1, and EP/K039466/1).

Acknowledgment

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

Is there **Primary Data** to be associated with this manuscript? Click here, then the arrow, and choose YES or NO.

References

(1) P. E. Eaton, T. W. Cole, *J. Am. Chem. Soc.* **1964**, *86*, 962–964.

(2) M. Zhang, P. E. Eaton, R. Gilardi, *Angew. Chem. Int. Ed.* **2000**, *39*, 401–404.

(3) P. E. Eaton, *Angew. Chem. Int. Ed.* **1992**, *31*, 1421–1436.

(4) L. K. Macreadie, E. J. Mensforth, R. Babarao, K. Konstas, S. G. Telfer, C. M. Doherty, J. Tsanaktsidis, S. R. Batten, M. R. Hill, *J. Am. Chem. Soc.* **2019**, *141*, 3828–3832.

(5) H.-T. Huang, L. Zhu, M. D. Ward, T. Wang, B. Chen, B. L. Chaloux, Q. Wang, A. Biswas, J. L. Gray, B. Kuei, et al., *J. Am. Chem. Soc.* **2020**, jacs.9b12352.

(6) G. M. Locke, S. S. R. Bernhard, M. O. Senge, *Chem. - A Eur. J.* **2019**, *25*, 4590–4647.

(7) K. F. Biegasiewicz, J. R. Griffiths, G. P. Savage, J. Tsanaktsidis, R. Priefer, *Chem. Rev.* **2015**, *115*, 6719–6745.

(8) (a) K. J. Flanagan, S. S. R. Bernhard, S. Plunkett, M. O. Senge, *Chem. - A Eur. J.* **2019**, *25*, 6941–6954. (b) N. Grover, G. M. Locke, K. J. Flanagan, M. H. R. Beh, A. Thompson, M. O. Senge, *Chem. - A Eur. J.* **2020**, *26*, 2405–2416.

(9) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756.

(10) B. A. Chalmers, H. Xing, S. Houston, C. Clark, S. Ghassabian, A. Kuo, B. Cao, A. Reitsma, C.-E. P. Murray, J. E. Stok, et al., *Angew. Chem. Int. Ed.* **2016**, *55*, 3580–3585.

(11) E. Tse, S. Houston, C. Williams, G. P. Savage, L. Rendina, I. Hallyburton, M. Anderson, R. Sharma, G. Walker, R. S. Obach, et al., *J. Med. Chem.* **2020**. DOI 10.1021/acs.jmedchem.0c00746.

(12) P. K. Mykhailiuk, *Org. Biomol. Chem.* **2019**, *17*, 2839–2849.

(13) T. M. Sodano, L. A. Combee, C. R. J. Stephenson, *ACS Med. Chem. Lett.* **2020**,

(14) (a) T. A. Reekie, C. M. Williams, L. M. Rendina, M. Kassiou, *J. Med. Chem.* **2019**, *62*, 1078–1095. (b)J. Wlochal, R. D. M. Davies, J. Burton, *Org. Lett.* **2014**, *16*, 4094–4097.

(15) K. C. Nicolaou, D. Vourloumis, S. Totokotsopoulos, A. Papakyriakou, H. Karsunky, H. Fernando, J. Gavrilyuk, D. Webb, A. F. Stepan, *ChemMedChem* **2016**, *11*, 31–37.

(16) S. D. Houston, T. Fahrenhorst-Jones, H. Xing, B. A. Chalmers, M. L. Sykes, J. E. Stok, C. Farfan Soto, J. M. Burns, P. V. Bernhardt, J. J. De Voss, et al., *Org. Biomol. Chem.* **2019**, *17*, 6790–6798.

(17) J. Joubert, W. J. Geldenhuys, C. J. VanderSchyf, D. W. Oliver, H. G. Kruger, T. Govender, S. F. Malan, *ChemMedChem* **2012**, *7*, 375–384.

(18) J. J. Danon, T. A. Reekie, M. Kassiou, *Trends Chem.* **2019**, *1*, 612–624.

(19) S. M. Wilkinson, H. Gunosewoyo, M. L. Barron, A. Boucher, M. McDonnell, P. Turner, D. E. Morrison, M. R. Bennett, I. S. McGregor, L. M. Rendina, et al., *ACS Chem. Neurosci.* **2014**, *5*, 335–339.

(20) N. B. Chapman, J. M. Key, K. J. Toyne, *J. Org. Chem.* **1970**, *35*, 3860–3867.

(21) C. H. DePuy, B. W. Ponder, J. D. Fitzpatrick, *J. Org. Chem.* **1964**, *29*, 3508–3510.

(22) M. Bliese, J. Tsanaktsidis, *Aust. J. Chem.* **1997**, *50*, 189–192.

(23) M. J. Falkiner, S. W. Littler, K. J. McRae, G. P. Savage, J. Tsanaktsidis, *Org. Process Res. Dev.* **2013**, *17*, 1503–1509.

(24) J. P. Knowles, L. D. Elliott, K. I. Booker-Milburn, *Beilstein J. Org. Chem.* **2012**, *8*, 2025–2052.

(25) P. E. Eaton, Y. Xiong, J. P. Zhou, *J. Org. Chem.* **1992**, *57*, 4277–4281.

(26) (a) Y. Su, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. - A Eur. J.* **2014**, *20*, 10562–10589. (b) D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Rev.* **2016**, *116*, 10276–10341.

(27) T. Aillet, K. Loubiere, O. Dechy-Cabaret, L. Prat, *Chem. Eng. Process. Process Intensif.* **2013**, *64*, 38–47.

(28) G. Y. Bényei, I. Jalsovszky, C. Slugovc, G. Trimmel, G. Pelzl, A. Vajda, N. Éber, K. Fodor-Csorba, *Liq. Cryst.* **2005**, *32*, 197–205.

(29) D. C. Harrowven, M. Mohamed, T. P. Gonçalves, R. J. Whitby, D. Bolien, H. F. Sneddon, *Angew. Chem. Int. Ed.* **2012**, *51*, 4405–4408.

(30) (a) M. A. Dallaston, J. S. Brusnahan, C. Wall, C. M. Williams, *Chem. - A Eur. J.* **2019**, *25*, 8344–8352. (b) M. A. Dallaston, S. D. Houston, C. M. Williams, *Chem. - A Eur. J.* **2020**, 11966–11970.

(31) M. L. Ingalsbe, J. D. St. Denis, J. L. Gleason, G. P. Savage, R. Priefer, *Synthesis.* **2010**, 98–102.