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Pilot-Scale Production of Dimethyl 1,4-Cubanedicarboxylate

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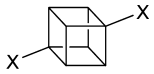
Supporting Information

ABSTRACT: A scalable process for the preparation of high purity dimethyl 1,4-cubanedicarboxylate (**3**) is reported. The work described herein builds on previous synthetic work from this and other laboratories, to provide a reliable process that can be used to prepare multigram quantities of **3** in a partially telescoped, 8 step process, with minimal purification of intermediates.

INTRODUCTION

The allure of molecules with structures that differ significantly from those typically produced by terrestrial organisms has provided tremendous impetus for chemists to attempt their synthesis, explore their physical properties and chemical reactivity, and investigate their practical applications.[1−3] The C_8H_8 hydrocarbon molecule, cubane (**1**) (Figure 1), the second



1 X = H
2 X = CO_2H
3 X = CO_2CH_3

Figure 1. Cubane nucleus.

member of the five convex, uniform polyhedral, also known as the Platonic solids, is an example of such unusual molecules; it features eight carbon atoms in an essentially perfect cubic arrangement, and eight hydrogen atoms, one at each of the eight vertices, completing the valency requirements of carbon. The result is a compact, spherical molecular entity that belongs to the octahedral point group O_h and possesses cubic symmetry.[4] In its crystalline form it forms rhombic crystals.[5] Consistent with its high symmetry and hydrocarbon nature, it has a significant vapor pressure of 177 pa at 25 °C,[6] and boasts an unusually high density for a hydrocarbon molecule of 1.29 g/cm^3.[7] Moreover, this unique, distinctly unnatural geometry renders cubane thermodynamically unstable (ΔH_f = 144 kcal/mol) and highly strained (SE = 161.5 kcal/mol).[8,9] These characteristics notwithstanding, cubane (**1**) itself displays a remarkable kinetic stability capable of withstanding temperatures of up to 220 °C.[10−14]

Cubane (**1**) was the first of two of the Platonic solids to succumb to chemical synthesis,[15] the other being dodecahedrane.[16] Since its systematic synthesis by Eaton and Cole in 1964,[17] many of its derivatives have been prepared and investigated for a myriad of purposes, including as pharmaceuticals,[18−25] drug delivery vectors,[26−34] liquid crystals,[35,36] polymeric materials,[37−39] explosives, and fuels.[40−44] The most convenient synthetic access to the cubane ring system is through its 1,4-dicarboxylates, namely 1,4-cubanedicarboxylic acid (**2**) and dimethyl 1,4-cubanedicarboxylate (**3**). The work reported herein builds on previous synthetic work from this and other laboratories, and provides a reliable process that can be used to prepare kilogram quantities of the synthetically versatile dimethyl 1,4-cubanedicarboxylate (**3**).

BACKGROUND

As referred to above, the original synthesis of the cubane ring system was reported by Eaton and Cole in 1964, proceeding through the diacid **2**, but isolated and characterized as the corresponding dimethyl ester **3** (Scheme 1).[15,17] This sequence delivered **3**, for the first time, in eight discrete steps from 2-cyclopentenone (**4**), in an overall yield of about 12%; however, detailed experimental procedures were not provided. Tactically, there are three key synthetic elements to this remarkably elegant synthesis that understate the complexity of the final structure: (i) the highly *endo*-selective [4π+2π] Diels−Alder dimerization of the highly reactive 2-bromocyclopentadienone (**5**) producing the *endo*-dimer **6**, almost exclusively (Scheme 2); (ii) the [2π+2π] ene-enone photocyclization of **6**, producing **7** (Scheme 1); and (iii) the double Favorskii ring contraction of the cage dione **7** in the presence of hot aqueous alkali to produce the disodium salt of 1,4-dicarboxylic acid **2** (Scheme 3).

In 1970, Chapman and co-workers reported a modified protocol as outlined in Scheme 4.[45] In that report, several limitations of Eaton's original protocol were flagged. These included access to 2-cyclopentenone (**4**) on scale, the capricious nature of the brominated precursors leading to dicyclopentadione **6**, and the formation of the bisdimethyl ketal of **7**, rather than **7** itself, during the photocyclization process. Chapman's modified sequence starts with the cyclopentanone ethylene ketal (**8**), which was easily prepared from cyclopentanone. Tribromination of **8** with 3 equiv of molecular bromine in anhydrous 1,4-dioxane produced the tribromide **9**, upon which treatment with NaOMe in methanol afforded the bisethylene ketal dimer **10**, through the transient bromocyclopentadiene ketal **13**. Selective monodeprotection of the less strained enone ketal in **10** with concentrated HCl in THF at room temperature furnished the monoketal **11**. Irradiation of a solution of **11** in deoxygenated benzene, through quartz, with UV light produced by a Hanovia 450W medium-pressure Hg

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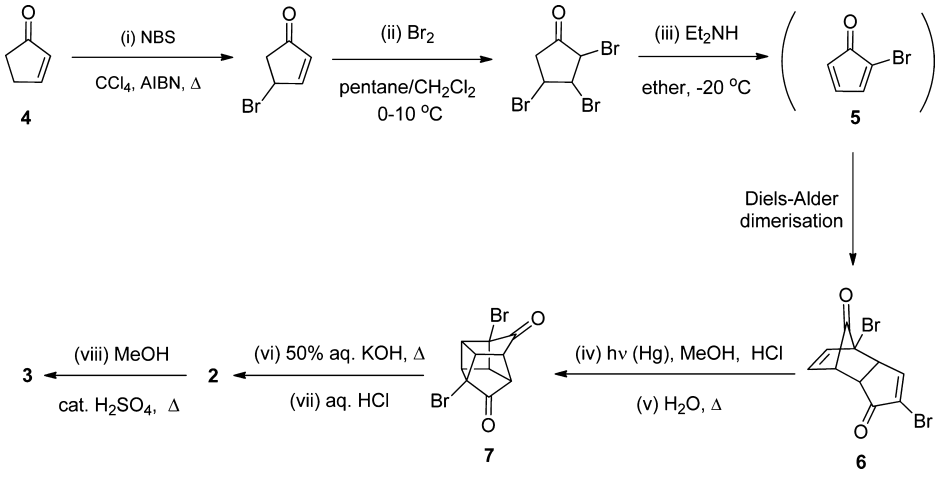
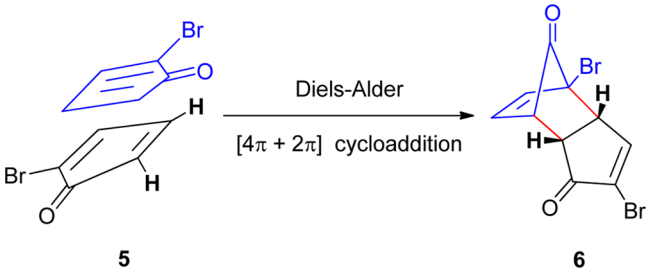
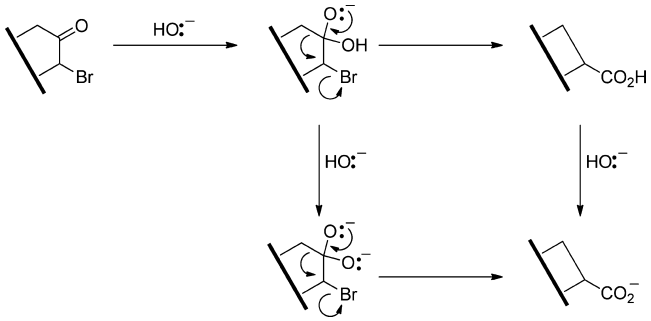
Scheme 1. Eaton Synthesis of the Cubane Ring System



Scheme 2. Diels−Alder Dimerization of 2-Bromocyclopentenone (5)



Scheme 3. Favorskii Ring Contraction: Semibenzilic Mechanism



lamp afforded the cage ketal **12**. Deketalization of **12** with concentrated H_2SO_4 delivered the cage dione **7**, which was then ring contracted to 1,4-cubanedicarboxylic acid (**2**), and isolated as the dimethyl ester **3** upon esterification. The overall yield of **3** obtained through this sequence was ∼3%. It should be noted, however, that Chapman encountered considerable difficulty with the double Favorskii ring contraction of **7** to **2**, with typical yields reported for this conversion being ∼10%, despite exploring a range of reaction conditions.[45] Shortly thereafter in 1972, Luh and Stock provided full experimental detail for the preparation of **3** using Eaton's original synthesis.[46] In this brief report the conversion of **7** to **2** was reported to proceed without complication, delivering **2** in ∼75% yield, upon treatment of **7** with 25% aqueous NaOH solution under reflux for 2 h.

Previous work from our laboratory brought together the key elements of the Eaton, and Chapman protocols to produce a reliable and practical laboratory scale process that provided ready access to **3** in tens of grams at a time, in an overall yields of ∼26%.[47] In that work key innovations were detailed, including (i) the double deketalization of the bisketal **10** using 98% H_2SO_4 and (ii) the telescoped conversion of the cage dione **7** to dimethyl 1,4-cubanedicarboxylate (**3**), in an overall yield of ∼47%. We now report on the translation of this latter protocol into a reliable and operationally simple pilot-scale process for the production of multigram quantities of dimethyl 1,4-cubanedicarboxylate (**3**).

■ RESULTS AND DISCUSSION

Our ongoing need for multigram quantities of dimethyl 1,4-cubanedicarboxylate (**3**) culminated in the translation of our laboratory scale protocol to our process facility with the aim of producing kilogram quantities of **3**. Accordingly, and as set out in Scheme 5, we have further refined, optimized, and intensified our laboratory scale process by minimizing the number of purification steps, and telescoping reactions wherever possible.

This work was performed with commercially sourced cyclopentanone ethylene ketal (**8**). Alternatively, **8** can be prepared from cyclopentanone using literature methods.[47−49] The tribromination of **8** to furnish **9** was best achieved using 3 equiv of molecular bromine in 1,4-dioxane as described by Chapman.[45] The active brominating agent in this reaction is believed to be the *in situ* formed 1,4-dioxane dibromide (DD).[50] The safety concerns associated with the use of 1,4-dioxane notwithstanding, DD is the reagent of choice as other brominating conditions, including pyridinium bromide perbromide, *N*-bromosuccinimide, and molecular bromine in various other solvents including acetonitrile, DMF, and trimethylphosphate were not capable of providing the tribromide **9**. Nevertheless, this process can be capricious if not executed under sufficiently anhydrous conditions. In the presence of water, deketalization of **8** and its bromination products occur readily during the bromination process, thereby reducing the yield of the desired tribromide **9**. This latter complication could be easily minimised through use of commercially available anhydrous 1,4-dioxane and molecular bromine, and with the maintenance of a dry nitrogen atmosphere during the reaction. It is worth noting that while **9** can be isolated, purified by crystallization from ethanol, and stored for prolonged periods at subambient temperatures (e.g., −10 °C), it is sensitive to moisture. Moreover, contact with

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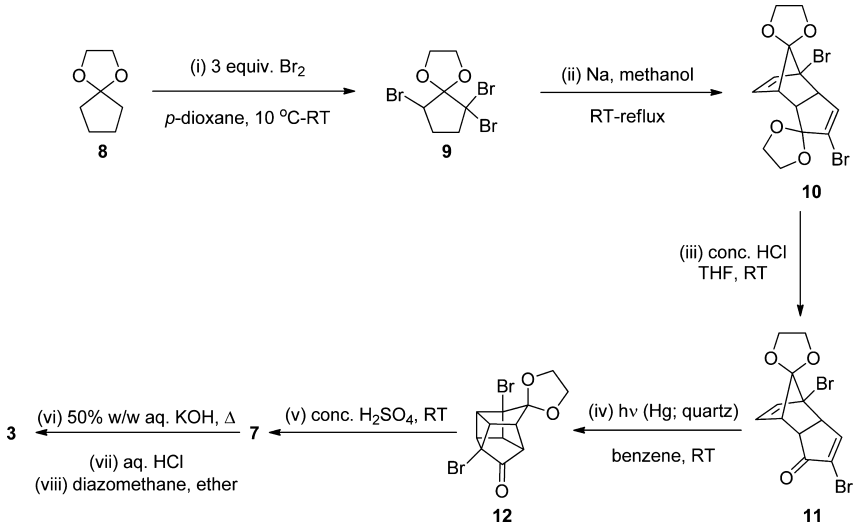
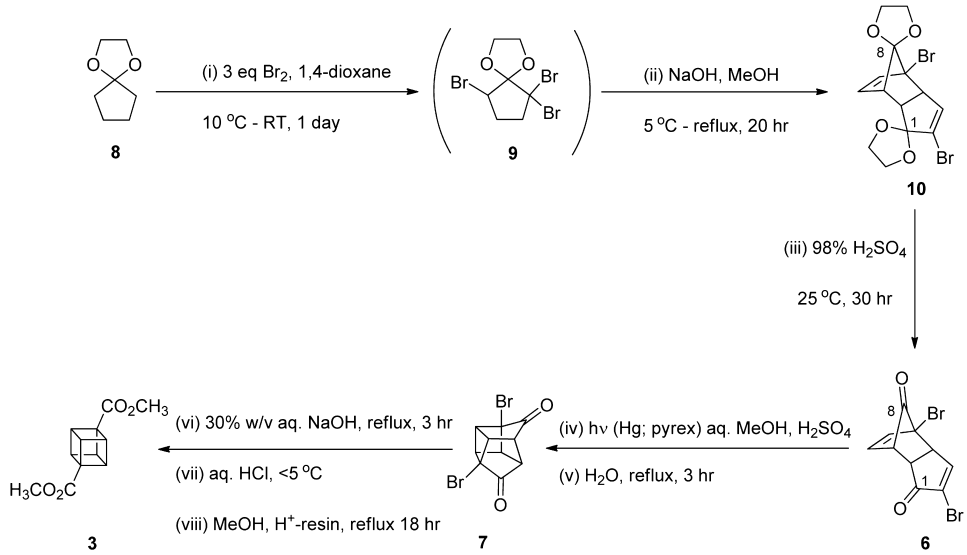
Scheme 4. Chapman Synthesis of Dimethyl 1,4-Cubanedicarboxylate (3)

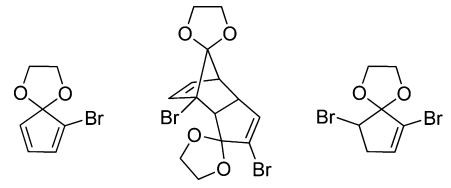


Scheme 5. Pilot-Scale Synthesis of Dimethyl 1,4-Cubanedicarboxylate (3)



metals must be especially avoided as its decomposition is significantly accelerated in their presence.

Armed with this knowledge we pursued an *in situ* conversion strategy of the tribromide **9** into the bisketal **10**. Guided by knowledge from our previous work[47] we reasoned that addition of excess methanolic NaOH to the crude bromination mixture would not only neutralize the dissolved conatal HBr present, but also facilitate double dehydrobromination of **9** to generate the highly reactive 2-bromocyclopentadienone ethylene ketal (**13**), which is known to produce the bisketal **10** through a highly stereoselective Diels–Alder dimerization (Scheme 2).[51] Indeed, this sequence was demonstrated enabling the isolation of the bisketal **10** in high purity and in good overall yields of ~80% (see Supporting Information). In this work, no attempt was made to remove the minor stereoisomer of **10**, **14**, that is also produced during this process.[52] Finally, it is worth noting that the first (i.e., fastest) dehydobromination is that which gives the dibromide **15**, and that this reaction proceeds rapidly at ambient temperatures. The second dehydrobromination to produce **13**, from **15**, is significantly slower and requires higher temperatures, thus the need to conduct the reaction under reflux. If desired, the dibromide **15** can be isolated by employing two effective equivalents of NaOH under milder conditions.



Conversion of the bisketal **10** into the dione **6** was successfully accomplished through exhaustive deketalization using 98% H_2SO_4 at 25 °C, as previously described.[47] Selective removal of the less strained enone-ketal in **10** (1-position in **10**) can be easily performed using milder conditions such as concentrated HCl in THF at room temperature;[45] however, removal of the more strained 8-ketal requires considerably harsher conditions, due to the strain of the resulting bridged ketone (8-position in **6**). This latter transformation is facilitated

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through the *in situ* destruction of the released ethylene glycol by H_2SO_4. While the use of 98% H_2SO_4 as both the solvent and reagent may seem counterintuitive, it nevertheless offers a simple and cost-effective solution that can be easily implemented in glass and acid-resistant metal reactors. It is important to note, however, that this reaction is quite temperature sensitive, with optimum conversions observed at 25 °C. The scale-up of this process was uneventful, providing access to **6** in ∼90% yields and in sufficient purity for use in the next step (see Supporting Information). While additional processing was not necessary for use in the next step of this sequence, recrystallization from ethyl acetate could be employed to furnish analytically pure samples of **6**.

The final sequence of this synthesis, encompassing five consecutive process steps, saw the conversion of the dione **6** to dimethyl ester **3**. The first step of this sequence involved the $[2\pi + 2\pi]$ ene-enone photocyclization of **6** to produce the cage dione **7** as a mixture of hydrates. The limited solubility of **6** in water, even in its hydrated form, necessitated the introduction of a water miscible cosolvent. This was achieved by irradiation of a dilute solution (0.157 M) of **6** in methanol/water (85:15), containing concentrated H_2SO_4 (15 mol %), with UV light from a medium-pressure Hg vapor lamp in a bespoke flow photolysis apparatus (Figure 2 and Supporting Information).

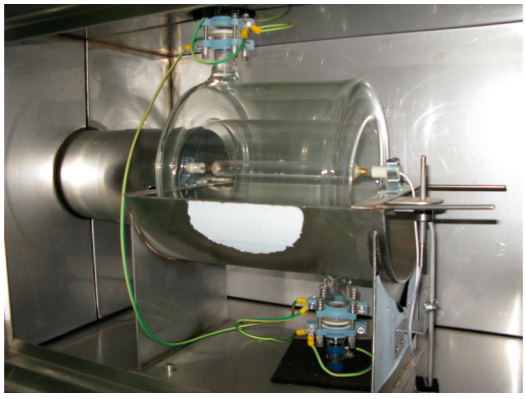

Figure 2. Pilot-scale photolysis apparatus comprising of a 6.4 L flow cell (Pyrex glass) with 2 diagonally opposed ports, a 2 kw medium pressure Hg vapor lamp, and fan forced air cooling, enclosed to prevent UV exposure.

The aqueous methanolic solution of **6** was initially held in a cooled storage vessel (10 °C) and pumped through the flow cell at rate of 4 L/min. Under these conditions, the conversion of **6** to **7** occurred at a rate of about 1 g per 4 min of irradiation, requiring a total irradiation time of 173 h. From a process perspective, this extended period of irradiation is not ideal, despite the success of this reaction. The long reaction time for this process can be attributed principally to the polychromatic nature of medium-pressure Hg vapor lamps, with only minor emissions in the critical region of 300 to 350 nm (see Supporting Information for UV spectrum of **6** under the conditions of the reaction). A better matched light source would be expected to significantly reduce irradiation time, and the concomitant waste of energy.

Once judged complete by ^{1}H NMR, evidenced by the disappearance of the characteristic olefinic resonances in the dione **6**, the reaction mixture was concentrated to dryness (45 °C at 60 mmHg) and the crude cage dione **7** used in the next step without further processing. Removal of the methanol was essential as its presence in significant quantities was deleterious to the subsequent Favorskii ring contraction. Moreover, this concentration process was helpful in hydrolyzing any dimethyl ketals of **7** that may have formed during the lengthy photocyclization process. To ensure complete hydrolysis of any remaining dimethyl ketals of **7** prior to the double Favorskii ring contraction of **7**, it was deemed prudent to heat the acidic residue in the presence of water for a further period (step 2).

Step 3 of this sequence saw the conversion of the crude cage dione **7** into the disodium salt of **2** through a double Favorskii ring contraction (Scheme 3). The original works from Eaton and Cole,[17] and Luh and Stock[46] reported that exposure of **7** to boiling aqueous NaOH solutions (50 and 25 wt %, respectively) were effective in converting **7** to **2**. Previous work from this laboratory verified these findings and recommended the use of 12 mL of 25% w/v of aqueous NaOH per gram of cage dione **7** (0.26 M in **7**).[47] In this work we used a 0.37 M solution of the crude cage dione **7**, 30% w/v aqueous NaOH, and a reaction time of 3 h to produce the cubane ring system as the disodium salt of the dicarboxylic acid **2**. These conditions represent a molar equivalency of NaOH to **7** of ∼20:1 (or ∼10:1 on a functional group basis) which is lower than that used in our laboratory scale process of ∼24:1. Careful acidification of the strongly basic Favorskii liquor with concentrated HCl acid afforded the diacid **2** as tan-brown solid (step 4). This process proved to be quite sensitive with reproducible results obtained when the temperature of the aqueous solution was maintained at between 0 and 5 °C during the addition of the concentrated HCl solution. In our laboratory scale process we were able to achieve this by adding the chilled basic solution to a freshly prepared mixture of concentrated HCl and ice chips. In the present case, however, the superior cooling and mixing capacity of our reactor allowed good control of the reaction conditions through slow addition of concentrated HCl solution to the cooled alkali liquor. The crude diacid **2** was recovered by filtration, dried, and used further without purification. If desired, the aqueous filtrate can be extracted with ethyl acetate and tetrahydrofuran (1:1 mixture) to recover additional, albeit small, quantities of the diacid **2**.

The final step of this sequence (step 5) involved the esterification of diacid **2** to produce the more chemically versatile and more easily purified dimethyl ester **3**. Treatment of crude diacid **2** with boiling methanol, in the presence of a strong acid resin, delivered **3** upon filtration to remove the resin, and evaporation of the methanol. Purification of the highly colored crude dimethyl ester **3** was best achieved through the combination of vacuum sublimation, and recrystallization from either acetonitrile or methanol, or a 1:1 mixture thereof. Attempts to purify crude **3** through crystallization alone were neither effective nor efficient, as removal of the highly colored impurities was possible only through vacuum sublimation. While technically less convenient to perform at scale, vacuum sublimation was extremely effective as a first-pass purification process of **3**. This final five step sequence, starting from **6** and culminating in the isolation of dimethyl 1,4-cubanedicarboxylate (**3**), provided the latter as a colorless crystalline solid in overall yields of ∼30%.

The highly strained (energetic) nature of the cubane ring system coupled with the process intensity of some of the latter processing steps warrants further comment in relation to the thermodynamic and kinetic stability of the cubanecarboxylates, **2** and **3**. Relative to cubane (**1**), the diacid **2** and its dimethyl

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ester **3** are significantly more thermodynamically stable as reflected by their heats of formation (ΔH_f) of −85.1 and −55.6 kcal/mol, respectively.[9,53] Both **2** and **3** are indefinitely stable at ambient temperatures as demonstrated by the passage of time in this and other laboratories. Differential scanning calorimetry (DSC) of dimethyl ester **3**, identified an endothermic phase transition (fusion) from 163.3 to 168.8 °C, with a peak at of 165.4 °C, which agrees well with literature melting point values obtained using conventional melting devices.[17,45−47] This event was followed by the onset of a significant exothermic event between 179.8 and 273.6 °C, as a result of decomposition. Integration of this part of the DSC chart gives an energy content of **3** of 1.31 × 10^3 J/g, and an energy density of 1.87 × 10^9 J/m^3 when combined with its density of 1.424 g/cm^3.[54] Thermal gravimetric analysis (TGA) of **3** showed the gradual loss of mass beginning upon fusion and ending at ∼260 °C (see Supporting Information for DSC and TGA charts). In the case of the diacid **2**, DSC indicated a melting event with a peak at 220.7 °C, which transitioned into a sharp exothermic event between 233.5 to 260.3 °C, as a result of decomposition. Integration of this part of the DSC chart provides an energy content of **2** of 1.47 × 10^3 J/g, and an energy density of 2.40 × 10^9 J/m^3 when combined with its density of 1.640 g/cm^3.[8,54] TGA of **2** revealed gradual mass loss beginning at 191.4 °C (see Supporting Information for DSC and TGA charts). This analysis clearly demonstrates that both **2** and **3** are stable at temperatures significantly above ambient, only decomposing at or above their melting points. Nevertheless, when using cubane compounds it is strongly recommended to avoid processing at elevated temperatures, particularly of crude reaction mixtures.

■ CONCLUSIONS

In this paper we have described a reliable and highly sequenced protocol capable of delivering dimethyl 1,4-cubanedicarboxylate (**3**) in multigram quantities in an overall yield of ∼22%, over 8 process steps from the ketal **8**. This protocol is operationally simple, requiring only limited purification interventions for all of the intermediates, and with the exception of the photocyclization and sublimation steps is easily amenable to further scaling. This method consolidates the key elements of Eaton and Cole's original synthesis of the cubane nucleus (Scheme 1), namely, the Diels−Alder dimerization of a brominated cyclopentadienone synthon (**5** or **13**), an intramolecular [2π+2π] ene-enone photocyclization, and a double Favorskii ring contraction, along with the latter Chapman (Scheme 4) and Tsanaktsidis innovations, into a streamlined method that can deliver multigram quantities of dimethyl 1,4-cubanedicarboxylate (**3**) (Scheme 5). It is our belief, and hope, that easy access to **3** in sizable quantities will encourage further exploration and experimentation with this fascinating molecular system.

■ EXPERIMENTAL SECTION

General. All reactions were carried out in dry Buchiglasuster glass-lined ChemReactor vessels, under an atmosphere of dry nitrogen, unless otherwise specified. Temperature control was achieved using an Engmann silicon oil heater/chiller (working range −70 to 220 °C), rated at 6.0 kW at −60 °C for cooling, and 24 kW for heating. UV light used for the photocyclization of **6** was generated using a BLV (UVE 022049) 2kw medium pressure Hg vapor lamp (ignition voltage 400 V; arc length 208 mm; diameter 22.5 mm; overall length 330 mm). The photolysis cell used was a 6.4 L annular vessel with an inner cylindrical wall, fabricated from Pyrex glass, with two diagonally opposed ports. The photolyzed solution was recirculated using a Husky double diaphragm pump Model D515 with polypropylene body through carbon impregnated Teflon tubing (3/4 in i.d.). Filtrations were performed using Hathernware vacuum ceramic Nutsche filter, through a nylon filter cloth (25 μm). The cyclopentanone ethylene ketal (**8**) used in this work was purchased from either Rose Scientific or Sigma-Aldrich and was used as received, whereas anhydrous dioxane and bromine were purchased from Sigma-Aldrich. All other materials used in this work were purchased from Sigma-Aldrich and used as received without further purification. Reactions were monitored for progress and purity by ^{1}H and ^{13}C NMR. NMR spectra were acquired in either $CDCl_3$ or d_6-DMSO on Bruker BioSpin Av400 NMR spectrometer equipped with either a 5 mm ^{1}H-BB inverse broadband probe operating at 400.13 MHz for ^{1}H acquisition. The data were acquired and processed in Bruker BioSpin TopSpin. The samples were maintained at 25 °C during acquisition. ^{1}H spectra are referenced to the residual protonated peak of the deuterated solvent while ^{13}C spectra are referenced to the deuterated solvent. The UV spectrum of dione **6** were recorded using an Agilent 8453 UV−vis photodiode array spectrometer. The sample was measured using a 1 cm path length cuvette, with methanol/water (85:5) as solvent, in the presence of catalytic sulfuric acid. Differential scanning calorimetry (DSC) analyses were conducted on a Mettler Toledo 821. The module was calibrated with indium/zinc total method. Samples were run in a DSC mode with an underlying heating rate of 10 °C per minute. Nitrogen was used as the environmental gas. Samples were encapsulated in lightweight aluminium pans (13 mg). A sample size of between 2 and 10 mg was used. Thermogravimetric analysis (TGA) was conducted on a Mettler Toledo TGA/STDA851 with *Star Software* version 9. Samples were run with a heating rate of 10 °C per minute. Samples were placed in a 70 μm alumina pan. Sample size of between 10 and 20 mg was used.

*endo-2,4-Dibromdicyclopentadiene-1,8-dione Bisethylene Ketal (**10**).* In a dry 100 L glass reactor, a solution of cyclopentanone ethylene ketal (**8**) (3 kg, 23.4 mol) was added to anhydrous 1,4-dioxane (12 L) under nitrogen. To this solution, molecular bromine (12 kg, 75 mol) was added dropwise (5 h), with stirring (200 rpm), while maintaining the temperature of the reaction mixture at approximately 10 °C, under an atmosphere of nitrogen. The bromine was added directly into the stirred reaction mixture to avoid solids formation (dioxane dibromide) on the sides of the reactor. After the addition was complete, the red-brown mixture was warmed to room temperature and left stirring for a further 20 h, with a purge of nitrogen through the reactor to facilitate removal of HBr which was trapped in a liquid scrubber containing a solution of 5% aqueous NaOH. The stirred brominated reaction mixture was cooled to 5 °C and treated with a solution of sodium hydroxide (5.2 kg, 130 mol) in methanol (26 L) over a period of 4−5 h, while maintaining temperature of the reaction mixture at or below 5 °C. After the addition was complete, the mixture was heated under reflux for 20 h. The resulting dark brown mixture was then cooled to room temperature and pumped out of the reactor into a separate vessel containing a mixture of ice and water (60 L) while being stirred. The resultant slurry was filtered under vacuum and the collected solid material washed successively with water (40 L), and cold methanol (2 L). This solid was

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then air-dried on the filter under suction, and then to constant weight in an oven at 40 °C, leaving behind the crude bisketal **10** (3793g, 80%) as pale beige solid, which was used in the next step without further processing.

*endo-2,4-Dibromodicyclopentadiene-1,8-dione (**6**).* A 100 L glass reactor was charged with 98% H_2SO_4 (12.5 L) at ambient temperature. The crude bisketal **10** (3793 kg, 9.3 mol) was then added in portions over a period of 1 h, with stirring (150 rpm), while maintaining the temperature of the reaction mixture at 25 °C. The resulting reaction mixture was then stirred for 30 h at 25 °C; the progress of the reaction was monitored by ^{1}H NMR for the complete absence of ketal-proton resonances. Once judged complete, the reaction mixture was then run out into separate vessel containing a mixture of ice and water (40 L) while being stirred. The resultant slurry was filtered under vacuum. The solid collected was then washed successively with water (15 L), then air-dried on the filter under suction, and then to constant weight in an oven at 40 °C, affording the dione **6** (2773g, 93%) as a beige colored solid, which was used in the next step without further processing.

*Dimethyl 1,4-Cubanedicarboxylate (**3**).* The crude dione **6** (2.7 kg, 8.5 mol) was dissolved in methanol (47 L), water (8.5 L), and sulfuric acid (66 mL, 15 mol %) in a 100 L glass reactor (holding vessel) under an atmosphere of nitrogen, at 10 °C. This solution was then pumped continuously, using a diaphragm pump, at a rate of 4 L/min, through a 6.4 L photolysis cell while being irradiated with a 2 kw medium pressure Hg lamp, and then returned to the holding vessel, with the average residence time per pass being 1.6 min. During this time the temperature of the air cooled photolysis cell was maintained between 40 and 45 °C, whereas the temperature of the holding vessel was maintained at 25 °C. Irradiation was continued for a total of 173 h, after which time the olefinic resonances of **6** were no longer visible by ^{1}H NMR.

The crude photolyzed solution was then concentrated to dryness using a rotary evaporator (45 °C at 60 mm Hg), leaving behind the cage dione **7** (*ca.* 3 kg), as a gummy dark-brown solid.

The crude cage dione **7** was then dissolved in water (23 L) and transferred into a 100 L glass reactor, stirred (150 rpm), and heated under reflux for 3 h, to ensure hydrolysis of any dimethyl ketals of **7** that may have formed during photolysis, and then cooled to ambient temperature. Solid sodium hydroxide (6.7 kg) was then added in portions to the stirred solution, and the resulting alkali mixture heated under reflux for 3 h, then cooled to ambient temperature.

32% aqueous HCl (15 L) was then added slowly over several hours, with stirring (150 rpm), to the precooled (0 °C) aqueous alkali reaction mixture; during this addition the temperature was maintained at or below 5 °C. The acidified mixture (pH 1−2) was left stirring overnight at room temperature and then filtered under vacuum. The collected solid was then dried on the filter under suction for several hours. The solid filter cake was washed with ice-cold water (2 × 5 L) and dried in the oven at 45 °C, until constant weight, leaving behind the crude diacid **2** (1287 g) as a dark brown solid.

A dry 100 L glass reactor was charged with the crude diacid **2** (1287 g), dry methanol (36 L), and Dowex ion-exchange resin 50WX8−100 (176 g) that was prewashed with 1 L of methanol. This mixture was then stirred (150 rpm), and heated under reflux for 18 h under an atmosphere of nitrogen. The mixture was then cooled to room temperature and filtered to remove the resin. The methanol solution mixture was then evaporated to dryness using a rotary evaporator (45 °C at 45 mmHg) leaving behind the crude diester **3** (863 g) as a dark brown solid. Purification by sublimation (100−120 °C/0.01 mmHg), followed by recrystallization from acetonitrile furnished the diester **3** (560 g, 30%), as a colorless solid, mp 164.5 °C (lit. 161−162 °C).[47] ^{1}H NMR δ: 3.7, s, 6H 4.24, s, 6H, ring protons. ^{13}C NMR δ: 47.03, 51.55, 55.77, 171.89.

■ ASSOCIATED CONTENT

Supporting Information

Analytical data of crude and purified products S2-7 UV spectrum of dione 6 S8 DSC and TGA charts of 2 and 3 S9-10 Drawings of the photolysis rig and flow cell. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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