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Cite this: *Chem. Commun.*, 2023, **59**, 7971

Received 3rd May 2023,
Accepted 30th May 2023

DOI: 10.1039/d3cc02164e

rsc.li/chemcomm

A practical synthesis of 1,3-disubstituted cubane derivatives†

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A robust multigram-scale synthesis of 1,3-disubstituted cubanes (previously only available on milligram-scale) is reported. The approach exploits a readily available enone intermediate previously used for the synthesis of 1,4-disubstituted cubanes, by introducing a novel Wharton transposition to access useful quantities of 1,3-disubstituted cubanes for diverse applications.

Ever since Eaton and Cole's landmark synthesis of the cubane system,[1] chemists have been fascinated by this highly strained, non-natural cage motif.[2] More recently, attention has turned to developing applications of cubanes, particularly within medicinal chemistry, where it has been suggested that cubanes may act as bioisosteres for the benzene ring.[3–5] However, the vast majority of work on the applications of cubanes has been focused on 1,4-disubstituted cubanes (Fig. 1), as only these derivatives are available on multigram-scale. Other substitution patterns (such as 1,3-disubstituted cubanes), are accessible only in milligram quantities, and/or their synthesis requires long synthetic sequences often starting from the corresponding 1,4-disubstituted derivatives. The lack of access to multigram quantities of cubanes that bear different substitution patterns continues to preclude a full evaluation of the potential of cubanes in medicinal chemistry (as well as other areas), thus new synthetic approaches are required to bridge this gap.

Only two distinct direct routes to 1,3-disubstituted cubanes have been reported. The 3-step Pettit route (Scheme 1; A) features cyclobutadiene (**2**) as a key reagent, which undergoes Diels–Alder reaction with dibromoquinone **1**.[6] This is a particularly elegant and extremely concise route, but is not scalable, as it relies on the cyclobutadieneiron(tricarbonyl) complex (**6**), which is not commercial, is highly toxic and must be synthesised from expensive precursors.[7]

The Pettit approach was very recently revisited by MacMillan and co-workers,[4] exploiting bicyclic diazetidine **7**[8] as a new cyclobutadiene precursor. However, cyclobutadiene is very reactive and cycloadduct **3** is air- and moisture-sensitive, thus the route is feasible only on small scales (the sequence was demonstrated on 1 mmol scale), limiting its practicality. On the other hand, Ueda and co-workers showed that enone **9b** could be converted to cubane **5** (Scheme 1; B),[9] but this route is not viable for scale-up, due to the difficulty in accessing the key enone **9b** in appreciable quantities – it was obtained in only 4.5% yield (after exhaustive chromatography) as a side product of the synthesis of the regioisomeric enone **9a** (a precursor to 1,4-cubane dicarboxylate **10**, and available on kilogram scale).

Herein, we demonstrate a robust approach to **5** that allows the straightforward multigram-scale synthesis of 1,3-cubane diester **11** as well as various novel 1,3-disubstituted cubane derivatives. A key component of our approach is the 1,3-transposition of enone **9a** into enone **9b**, thus enabling the preparation of both 1,4- and 1,3-disubstituted cubanes from a common, easily accessible intermediate.

To start with, enone **9a** was prepared from cyclopentanone according to Tsanaktsidis's pilot scale synthesis[10] using standard laboratory glassware, followed by selective mono-deketalisation.[11] The synthesis was routinely carried out on scales of several hundred grams (see the ESI† for details). **9a** has previously been used in the synthesis of cubane 1,4-dicarboxylic acid,[12] and to access the corresponding 1,3-disubstituted cubanes, we envisaged converting **9a** into its isomeric enone **9b** *via* a Wharton transposition sequence.[13] Thus, nucleophilic epoxidation of enone **9a** gave epoxide **12** as a single diastereoisomer in essentially quantitative yield, with no purification required (Scheme 1). The subsequent Wharton reaction required some optimisation, since in addition to **13**, the corresponding debrominated allylic alcohol was produced in varying amounts depending on the reaction conditions. Limiting the number of equivalents of hydrazine employed

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† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d3cc02164e

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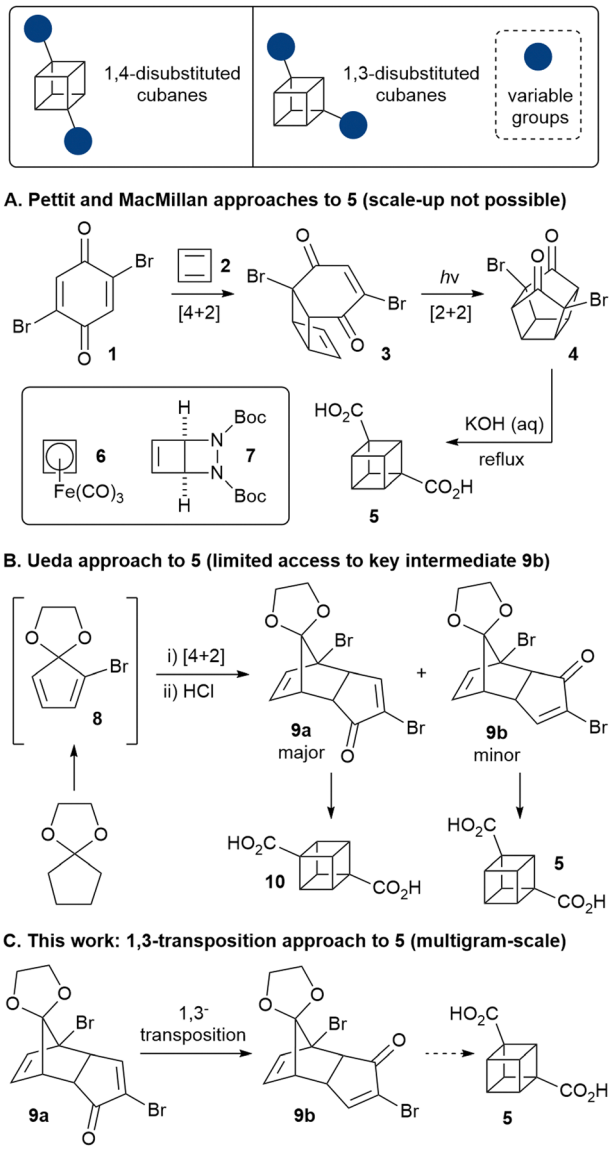
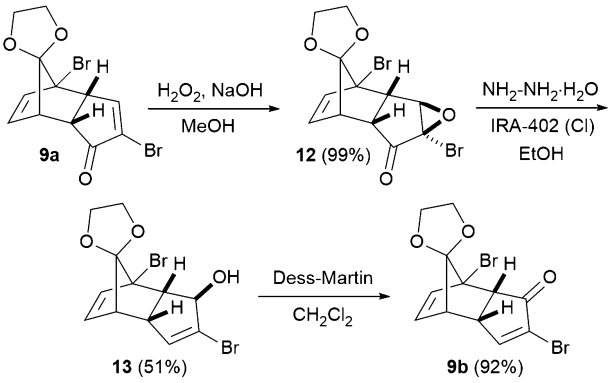
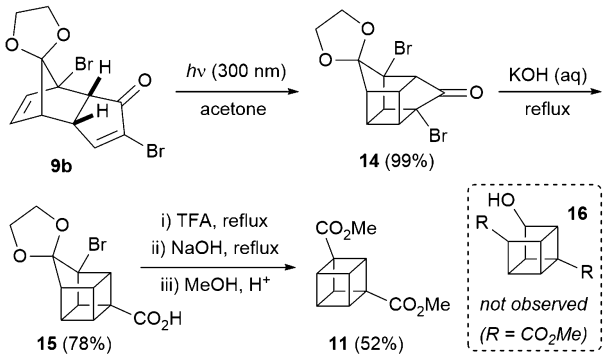


Fig. 1 Disubstituted cubanes; previous synthetic approaches to 1,3-disubstituted cubanes (A/B); this work (C).



Scheme 1 1,3-Transposition sequence to convert enone **9a** into enone **9b**.



Scheme 2 Conversion of enone **9b** into dimethyl 1,3-cubane dicarboxylate **11**.

largely suppressed the debromination, but slowed the reaction. Thus, the optimized conditions involved gentle heating of a solution of **12** and hydrazine in ethanol in the presence of an basic resin for 72 hours, furnishing allylic alcohol **13** in 51% yield. Subsequent oxidation using Dess-Martin periodinane gave enone **9b** in 92% yield, with the 3-step Wharton transposition sequence being carried out successfully on decagram scale.

Next, enone **9b** underwent facile [2+2] photocycloaddition upon irradiation at 300 nm, in acetone as both solvent and triplet sensitiser (Scheme 2). The reaction was performed on decagram scale and cycloadduct **14** was obtained in essentially quantitative yield after simple evaporation of the solvent. As previously noted by Ueda,[9] attempts to effect a double Favorskii-type ring contraction (after deketalisation of **14**) failed to yield diacid **5**, hence two separate ring contraction reactions were carried out. Acid **15** was obtained in 78% yield upon heating in aqueous sodium hydroxide, and deprotection of the ketal in **15** was best performed by heating in trifluoroacetic acid. Attempts to perform this deprotection in sulfuric acid (as is common in the 1,4-cubane series[10] and as reported by Ueda on small scales for the 1,3-cubane[9]) resulted in significant decomposition and an arduous aqueous extraction on multigram scales; pleasingly, both issues could be avoided simply by employing trifluoroacetic acid. The crude product was taken on directly into the second Favorskii-type ring contraction, which took place under more forcing conditions, and acid-mediated esterification of the resulting diacid in methanol gave 1,3-cubane diester **11** in 52% yield over the three steps – a significant improvement on the 25% yield obtained previously.[9] Interestingly, Ueda and co-workers obtained a ~1 : 1 mixture of **11** and open-cage derivative **16** (which presumably derives from initial Haller–Bauer reaction[14] instead of closure of the cubane), thus decreasing the overall yield of cubane **11**. This undesired reactivity was also observed under our conditions through monitoring the ring contraction reaction by ^{1}H NMR spectroscopy (with solvent suppression), but to our surprise, the cubane core was regenerated under the acidic esterification conditions employed, and no trace of **16** was detected. Thus, the choice of esterification conditions is crucial in optimising the yield of **11**, with the milder esterification conditions chosen by the Ueda group (diazomethane) leading to significant amounts of the undesired open-cage product **16**.

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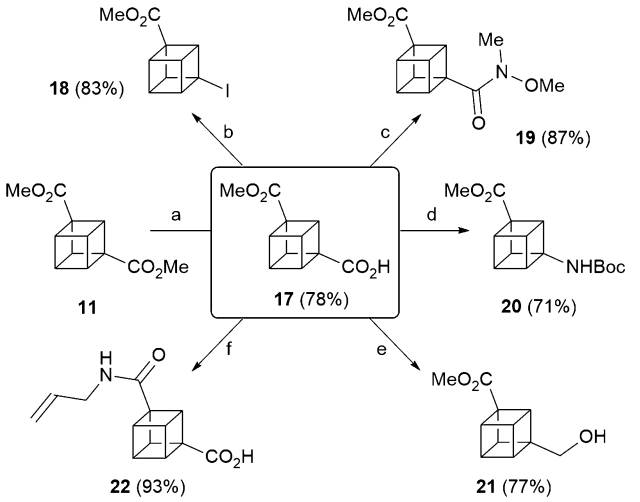

Scheme 3 Selected synthetic manipulations of **17** to give five novel 1,3-disubstituted cubane derivatives. [a]NaOH (aq), MeOH [b]$PhI(OAc)_2$, I_2, C_6H_6, reflux [c]CDI, MeNH(OMe)·HCl, CH_2Cl_2 [d]DPPA, Et_3N, [t]BuOH, reflux [e]BH_3·SMe_2, THF, 0 °C to rt [f]Allylamine, reflux. CDI = carbonyldiimidazole, DPPA = diphenylphosphorylazide.

Finally, 1,3-cubane diester **11** underwent selective monosaponification to give carboxylic acid **17** (Scheme 3), which is a versatile intermediate *en route* to diverse 1,3-disubstituted cubanes. Thus, in addition to the cross-coupling methodology recently reported by the MacMillan group,[4] **17** also undergoes standard functional group interconversions, and five novel functionalised 1,3-disubstituted cubanes were prepared in short order, through iodination of the carboxylic acid moiety to give **18**, formation of the corresponding Weinreb amide **19**, Curtius rearrangement to give **20**, and selective borane-mediated reduction to give alcohol **21**. In addition, aminolysis of the ester moiety in **17** through heating in allylamine gave amide **22** in excellent yield (Scheme 3).

In summary, we have developed a multigram-scale synthesis of dimethyl 1,3-cubane dicarboxylate (**11**), which was previously available only on milligram scale, and demonstrated that **11** can be readily converted into a variety of different 1,3-disubstituted cubane derivatives *via* acid-ester intermediate **17**. Key to the success of the approach was the development of a Wharton 1,3-transposition sequence of readily available enone **9a** into enone **9b**, such that both 1,4- and 1,3-disubstituted cubanes can now be easily prepared from a single intermediate. This work will expedite investigations into the applications of 1,3-disubstituted cubanes, which have so far been frustrated by the paucity of accessible 1,3-disubstituted cubanes. Now that appreciable quantities are available, applications are envisaged in particular within medicinal chemistry (*e.g.* as bioisosteres for *meta*-substituted benzene rings), but diverse applications can easily be envisaged in a broad range of other areas (for example, in materials chemistry, supramolecular chemistry and biochemistry).

This work was supported by funding from North West Cancer Research (LFSL2018-23, Studentship to MCA).

Conflicts of interest

There are no conflicts to declare.

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