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Cubanes in Medicinal Chemistry: Synthesis of Functionalized Building Blocks

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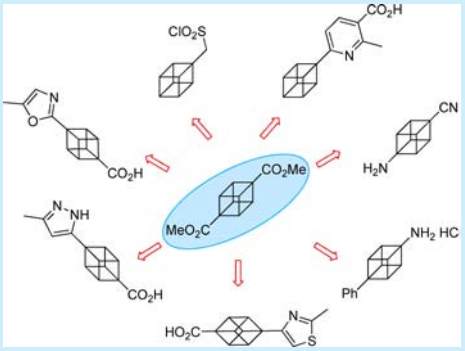
Supporting Information

ABSTRACT: A collection of novel, pharmaceutically relevant cubane-containing molecules has been prepared from the commercially available cubane-1,4-dimethylester. A range of synthetic methods have been applied to prepare these cubane building blocks with one or two functional handles to allow easy incorporation into existing medicinal chemistry programs.



Medicinal chemists are continually striving to reduce the attrition rates of candidate drug molecules. Recent reports highlight complexity and, by extension, degree of saturation as a useful metric in predicting success.[1,2] This idea led us to consider the cubane framework as an alternative to the usual aromatic and heteroaromatic motifs routinely deployed in medicinal chemistry. As early as 1992, Eaton had discussed the potential use of cubane in the synthesis of new pharmaceuticals based on its rigid framework and size with respect to a *para*-disubstituted benzene ring (Figure 1).[3] Cubane's compact,

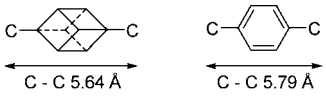


Figure 1. Body diagonal of (a) cubane and (b) xylene.

saturated three-dimensional structure offers different binding modes compared with aromatic systems and is incapable of undergoing intermolecular π-stacking, thereby potentially improving solubility. Furthermore, the cubane core has been shown to be a poor substrate in cytochrome P_{450} metabolic pathways,[4] which may lead to enhanced metabolic stability. The distance between substituents in 1,4-disubstituted cubanes is 5.64 Å[5] versus a *para*-substituted phenyl ring of 5.79 Å,[6] which suggests a potential use for cubane as a phenyl ring isostere (Figure 1).

Despite being known since 1964,[7,8] and extensively reviewed,[3,9] cubane[10] has found only limited use in medicinal chemistry. Such examples include work by Bashir-Hashemi,[11] where tetra-substituted cubane amides demonstrated anti-HIV properties. In another example, cubane carbinylamines synthesized by Eaton[12,13] were found to act as inhibitors of monoamine oxidase B (MAO B), an enzyme involved in Parkinson's disease.[14] In further work, Kassiou and co-workers found that a range of aromatic cubane carbinylamides[15,16] were effective against P2X7 ion channels which are involved in many biological functions.[17] Pellicciari, Pin, and co-workers[18] reported that carboxycubaneglycine was found to be a selective inhibitor of the glutamatergic pathway commonly affected in neurological disorders. Furthermore, Al Hussainy, Booij, and co-workers[19] developed cubane-containing ligands with high metabolic stability, as analogues of 5-hydroxytryptamine antagonists for use in positron emission tomography. We believe that the limited use of cubane in medicinal chemistry is largely due to the perceived synthetic complexity of this highly strained molecule coupled with its undesired high intrinsic energy that has been extensively investigated by the explosives industry.[3,9] A limited commercial supply chain for cubane-containing reagents has also served to discourage its use.

To further explore the utility of cubane in medicinal chemistry, we decided to develop the synthesis of gram quantities of cubane building blocks containing pharmaceutically relevant functionality that can be used in drug discovery programs. The most accessible starting point for cubane derivatization is the commercially available cubane-1,4-diester **1**.[7,10] From this, we planned to make building blocks conforming to the following four categories (Figure 2): (i) cubane as a terminal group with one functional handle for derivitization; (ii) bifunctional cubanes to be used as terminal groups or linkers; (iii) cubane heterocycles with a functional

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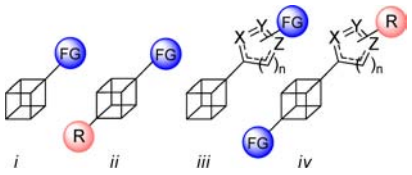
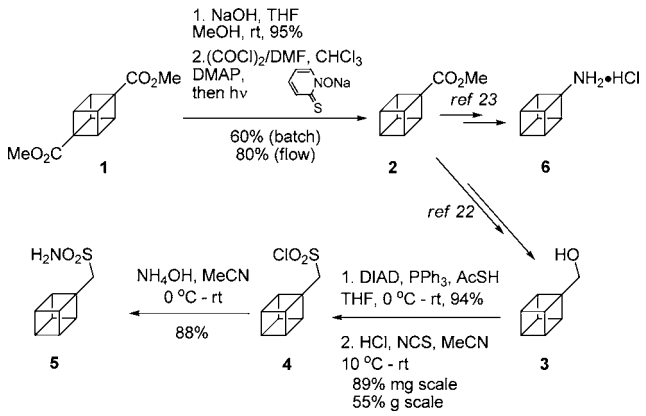


Figure 2. Different classes of cubane building blocks.

handle on the heterocycle; (iv) cubane heterocycles with a functional handle on the cubane.

The synthesis of the known monosubstituted cubane[20] **2** (Scheme 1) was accomplished in two steps from cubane-1,4-

Scheme 1. Preparation of Monosubstituted Cubane Building Blocks

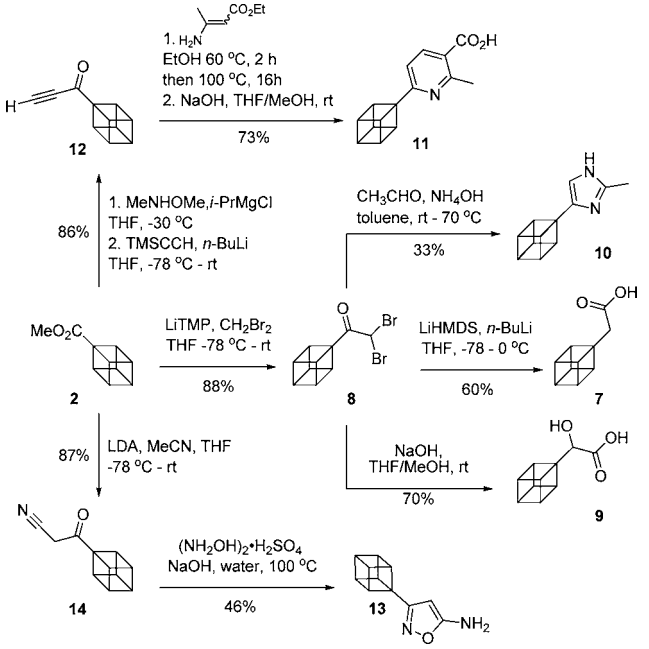


diester **1** using a modification of the Barton decarboxylation recently reported by Williams and Tsanaktsidis.[21,22] The synthesis began with hydrolysis of **1** to provide known acid ester[20] in 95% yield. Preparation of the intermediate acid chloride, followed by photoinduced decarboxylation of the corresponding thioester gave known cubane[20,21] **2** in 60% yield on a 40.0 mmol scale. Due to the requirements for a large quantity of the cubane monoester **2** and the scale limitation of the batch system, we investigated the synthesis of **2** in flow. A photoflow reactor was constructed in accordance with the method reported by Booker-Milburn,[23] and the subsequent decarboxylation delivered **2** in an improved 80% yield. Application of this method produced 10.0 g of monocubane ester **2** in less than 1 h.

With monoester **2** in hand, we looked to make our first set of terminal cubane building blocks. First, known cubanecarbinol **3**[24] was prepared in multigram scale and excellent yield via lithium borohydride reduction of **2**. Alcohol **3** was readily transformed into a novel thioester in 94% yield under mild Mitsunobu conditions, which on treatment with *N*-chlorosuccinimide and a substoichiometric amount of HCl gave access to gram quantities of the novel cubane sulfonyl **4** as a white crystalline, bench-stable solid in 89% yield. This intermediate could then be exposed to various nucleophiles, exemplified here by treatment with ammonia, which gave the novel cubane carbinylsulfonylamide **5** in good yield. Cubane amine hydrochloride **6**[25] was also prepared according to the recent report by Sklyarova et al.[26] in very good yield and large quantity.

We next looked to prepare the *C*-homologated analogue **7** of cubane carboxylic acid along with a number of related compounds (Scheme 2). For the preparation of **7** from **2**, we

Scheme 2. Synthesis of Various Building Blocks from Cubane Monoester with Functional Handle on Cubane or Heterocycle



chose a Kowalski homologation procedure, over the Arndt-Eistert reaction[24] due to safety concerns with the latter procedure. In the first step, dibromoketone **8** was prepared in 88% yield by treatment of monoester **2** with the anion of dibromomethane (Scheme 2). Dibromoketone **8** was then transformed[27,28] into cubane acetic acid **7**[24] in 60% yield by sequential addition of strong bases. Dibromoketone **8** also underwent basic hydrolysis[29] to α-hydroxy acid **9** in 70% yield.

The dibromoketone **8** could also be utilized to make our first example of a cubane heterocycle with a functional handle on the unsaturated ring. Treatment of **8** with acetaldehyde and ammonium hydroxide in toluene[30] at elevated temperatures provided cubane imidazole **10** in a moderate 33% yield.

Another example in this class of cubane is the pyridine-substituted cubane **11**. This was prepared using the Bohlmann-Rahtz reaction[31] as outlined in Scheme 2. Treatment of the Weinreb amide derived from ester **2** with the anion of TMS-acetylene gave novel ketone **12** in 86% yield. Condensation with ethyl 3-aminocrotonate was performed at 60 °C (microwave), followed by isomerization and cyclization at 100 °C (microwave) to form the pyridine core in 77% overall yield. Subsequent hydrolysis completed the synthesis of **11**.

In the final example of this type, cubane-isoxazole **13** was synthesized (Scheme 2) using a protocol for 5-amino isoxazole synthesis recently published by Mainolfi and co-workers.[32] Rowbottom and co-workers[33] used similar reaction conditions for the synthesis of a wide range of amino isoxazoles. Under the conditions investigated during this study, formation of the isomeric 3-amino isoxazole was not observed.

As a potential replacement for commonly used biaryl systems, we prepared known phenylcubane carboxylic acid **15**[12] and novel phenylcubane amine hydrochloride **16**. Synthesis of amine **16** (Scheme 3) utilized the protocol published by Eaton and co-workers,[12,20,34] whereby the diester **1** was converted into phenyl iodocubane which was subsequently converted into the carboxylic acid **15** on

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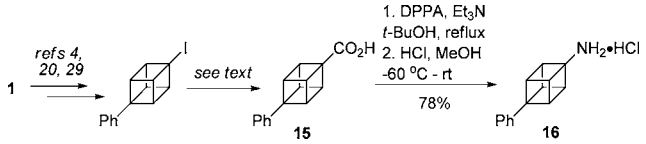
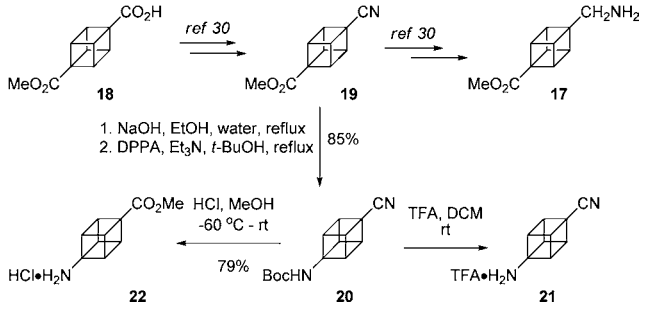
Scheme 3. Synthesis of 1,4-Disubstituted Cubane Building Blocks



treatment with *t*-BuLi and gaseous carbon dioxide. Our only modification to this route was the reverse addition of phenyl iodocubane to the solution of *t*-BuLi and use of solid carbon dioxide in place of the gas which gave phenylcubanecarboxylic acid **15**[12] in 89% yield. In situ azide formation with diphenylphosphoryl azide[34] and rearrangement upon heating provided the novel phenylcubane carbamate in very good yield; subsequent acid hydrolysis completed the synthesis of the novel 4-phenylcubane-1-amine hydrochloride **16**. This route delivered multigram quantities of both **15** and **16**.

Next, we prepared some examples of 1,4-bifunctional cubanes that would have additional potential to be used as linkers or cores in future work. The synthesis of known cubane carbinylamine **17** was accomplished in excellent 80% overall yield by application of the existing protocol[35] starting from cubane acid ester **18** with facile H-cube reduction of nitrile **19** using Adams' catalyst being the only modification (Scheme 4).

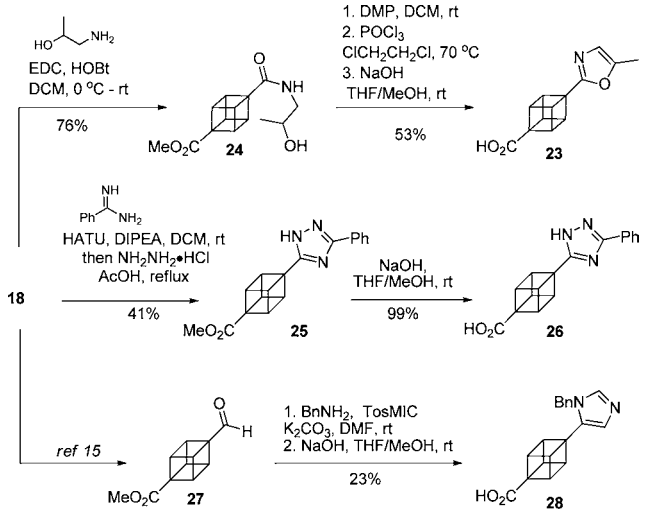
Scheme 4. Synthesis of 1,4-Disubstituted Cubane Building Blocks



The known cubane cyanoester **19** was further elaborated through hydrolysis and previously explored Yamada−Curtius reaction[34] to give the novel cyano-Boc-amine **20**. Deprotection of **20** with trifluoroacetic acid gave the desired novel cyanoamine trifluoroacetate salt **21**, which decomposed upon recrystallization. Alternatively, treatment of **20** with anhydrous HCl in methanol gave the hydrochloride salt of amino cubane ester **22**.

Lastly, we prepared examples of the final class of cubane heterocycles with a functional handle on the cubane. This necessitated building up the heterocycles from the cubane acid ester **18**, as cross-coupling chemistry using transition metals is documented to induce structural rearrangements in cubanes.[3,36] The synthesis of oxazole **23** outlined in Scheme 5 began with EDC coupling of 1-amino-2-propanol and **18** to give **24** in good yield. Dess-Martin oxidation of the novel amido alcohol **24** followed by dehydration gave the corresponding oxazole **23** in 53% overall yield. Subsequent hydrolysis of the methyl ester with sodium hydroxide delivered multigram quantities of the novel cubane oxazole acid **23**. Next, attention was directed to the synthesis of novel triazole **25** (Scheme 5), applying the method developed by Castanedo and co-workers.[37] Coupling

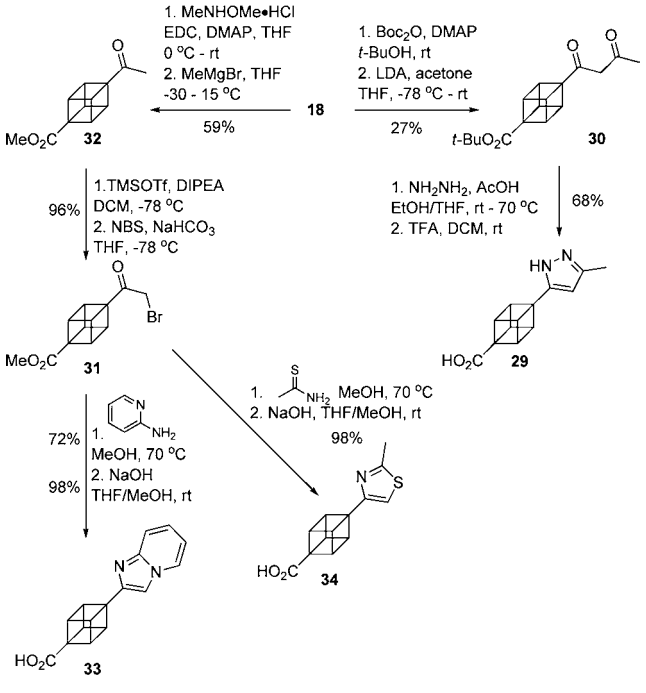
Scheme 5. Synthesis of 1,4-Disubstituted Cubane Building Blocks with Different Heterocycles



of benzamidine with **18** and treatment with hydrazine in acidic media gave **25**. Basic hydrolysis provided **26** in 40% overall yield. We also synthesized a disubstituted cubane-bearing imidazole by converting acid **18** into the known aldehyde **27**[18]. This underwent a van Leusen reaction with toluenesulfonylmethyl isocyanide[38] to give the corresponding imidazole in a moderate 27% yield, which could be hydrolyzed to the acid **28**.

The next heterocycle we looked to prepare was pyrazole **29**. As shown in Scheme 6, after the introduction of the bulky *t*-Bu ester onto **18**, reaction with the enolate of acetone gave the novel 1,3-diketone **30** in modest yield. Treatment of **30** with hydrazine hydrate under acidic conditions and acid cleavage of the ester with TFA completed the synthesis of pyrazole **29** in 68% overall yield.

Scheme 6. Synthesis of 1,4-Disubstituted Cubane Building Blocks with Different Heterocycles



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A useful intermediate in the preparation of cubane heterocycles, which was accessible by carbonyl group manipulation, was the α-bromoketone **31** which we prepared in four steps from **18**. Conversion of **18** into the corresponding Weinreb amide followed by reaction with MeMgBr gave the cubane ketoester **32**. Formation of the corresponding silyl enol ether followed by treatment with *N*-bromosuccinimide gave the novel α-bromoketone cubane **31** in good overall yield.

With ample quantities of **31** in hand, conversion to benzimidazole **33** and thiazole **34** was investigated. First, heating **31** and thioacetamidine in methanol under microwave conditions for 2 h allowed clean formation of the corresponding thiazole in 98% yield, which on hydrolysis delivered multigram quantities of the required cubane building block **34**. Similarly, treatment of **31** with 2-amino pyridine in methanol at reflux produced the cubane imidazo-pyridine heterocycle with basic hydrolysis completing the formation of **33** in excellent yield.

In conclusion, we have made a number of building blocks comprising mono- and bifunctionalized cubanes with a range of functional groups including novel heterocycles. Significantly, most were prepared in multigram quantities to allow their use in many drug discovery projects which should result in establishing the benefits or otherwise of cubane-containing molecules in medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds, including copies of ^{1}H and ^{13}C NMR spectra. 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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