Bioisosteres

Replacement of 1,4-disubstituted phenyl rings

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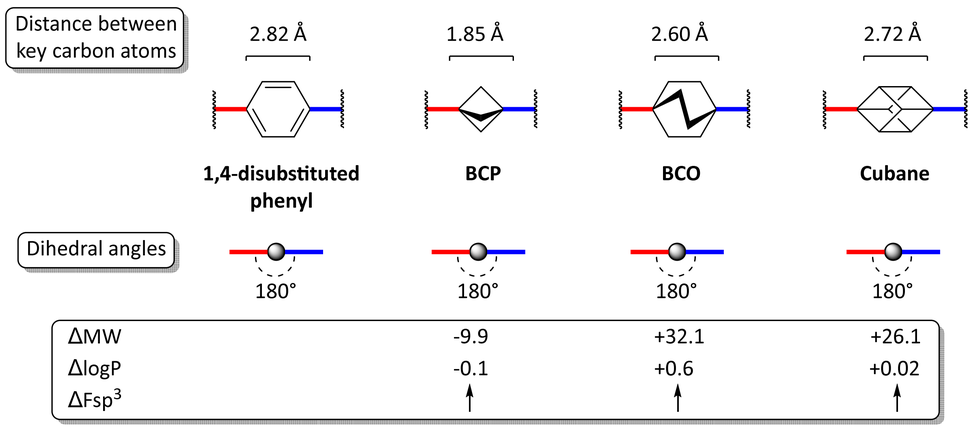
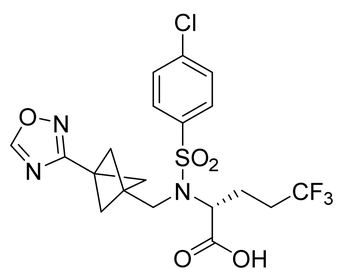
charnwood molecular
for the discovery

Overview

A 2017 paper by Auberson and co-workers reported a comprehensive comparison of the effects of replacing a *para*-substituted benzene with a bicyclo[1.1.1]pentane (BCP), a bicyclo[2.2.2]octane (BCO) and a cubane.[1] All three of these groups share similar spatial features to a 1,4-disubstituted phenyl ring, with identical dihedral angles making them interesting bioisoters. The effects of these groups on the solubility and non-specific binding characteristics of the compounds into which they were incorporated as replacements for a phenyl ring were evaluated and compared. An improvement in both parameters was observed for BCP and cubane but not for the BCO-containing derivative. Incorporation of these moieties can provide potential benefits in drug discovery programs and form part of the toolbox for medicinal chemists.

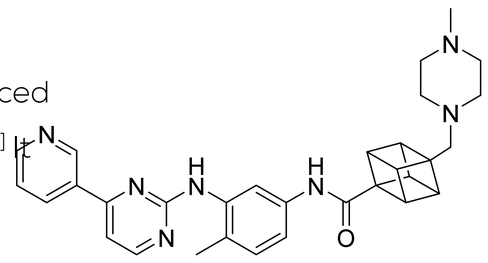


Examples



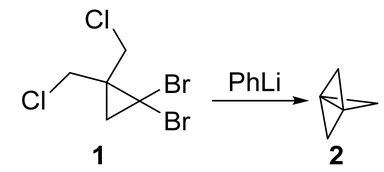
Stepan and co-workers showed that replacement of the central *para*-substituted fluorophenyl ring in a γ-secretase inhibitor with the BCP moiety resulted in significant improvements in aqueous solubility and passive permeability, with little change in the potency.[2]

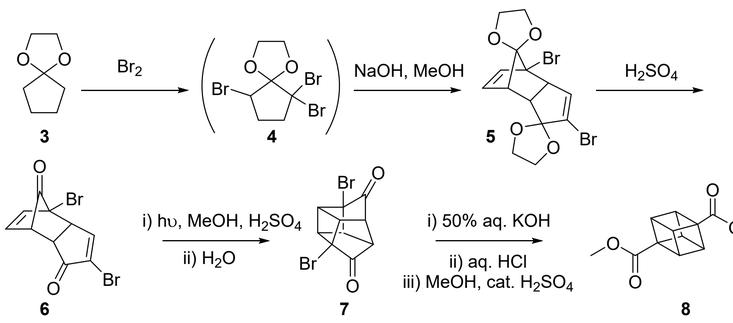
Nicolaou and co-workers synthesized a range of structural analogues of Imatinib, in which the *para*-substituted phenyl group was replaced with various non-aromatic structural motifs.[3] It was found that the cubane-containing derivative possessed the joint highest thermodynamic solubility as well as the highest potency against both cancer cell lines tested.



Synthesis

The most commonly used intermediate in the synthesis of BCP derivatives is [1.1.1]propellane 2.[4] The current, optimized method involves the treatment of compound 1 with two equivalents of phenyl lithium. This is then followed by co-distillation of 2 with diethyl ether.[5]



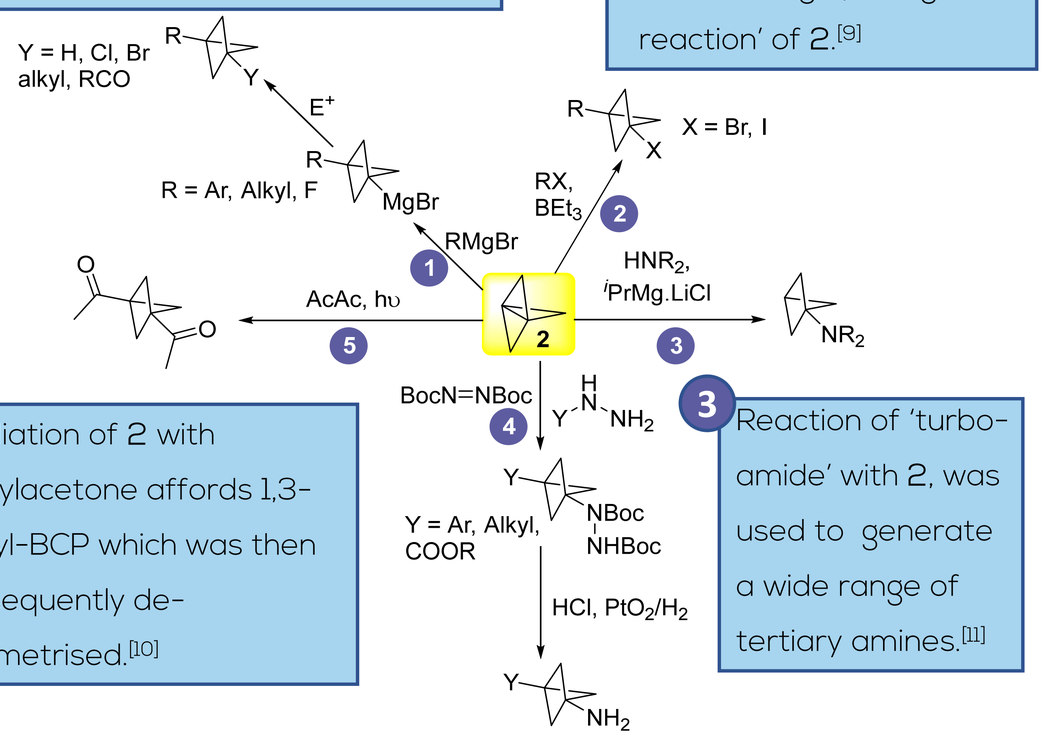


The majority of cubane-containing compounds are derived from compound 3.[6] Falkiner and co-workers published a pilot-scale synthesis (560 g) of building block 8 in 2003.[7] Affording an approximate yield of 22% over 8 process steps.

Functionalisation of BCP

1 2 can be reacted with a variety of Grignards followed by subsequent quenching with an electrophile to give 1,3-unsymmetrically substituted BCP derivatives.[8]

2 Iodo-BCP compounds were synthesised by 'triethylborane initiated atom transfer radical addition ring opening reaction' of 2.[9]



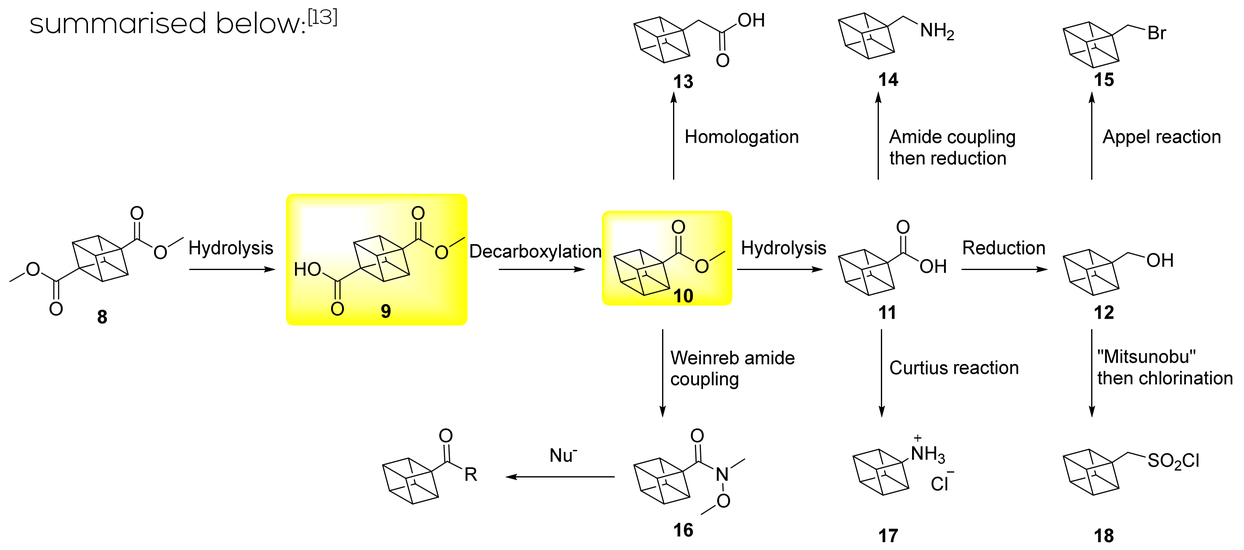
5 Irradiation of 2 with acetylacetone affords 1,3-diacyl-BCP which was then subsequently de-symmetrised.[10]

3 Reaction of 'turbo-amide' with 2, was used to generate a wide range of tertiary amines.[11]

4 The multi-component reaction between 2, di-tert-butyl-diazodicarboxylate and a variety of acyl-hydrazide derivatives afforded BCP-hydrazides which could be converted to amino-BCP via deprotection and hydrogenation.[12]

Functionalisation of cubane

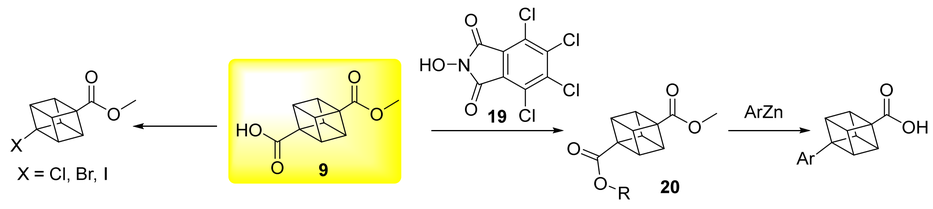
Compound 8 can be mono-functionalised by selective hydrolysis to give 9 followed by decarboxylation to 10. The remaining ester can be further functionalised as summarised below:[13]



Compound 9 can also be used to synthesis a range of 1,4-disubstituted cubanes exploiting chemistry analogous to that shown above.

Coupling between 9 and 19 followed by reaction with aryl zinc reagents in the presence of a nickel catalyst gave aryl substituted cubanes.

The acid of compound 9 can also be converted to Cl, Br or I through radical chemistry, providing another useful handle for further functionalisation.



Summary

BCP and cubane can be used as replacements for 1,4-disubstituted phenyl rings. These structures offer improvements in properties such as enhancements in solubility, permeability and stability. Multiple reaction have been investigated to derivatise BCP and cubane cores to provide a set of building blocks to allow these moieties to be incorporated into molecules.

References: [1] - ChemMedChem 2017, 12, 590-598, [2] - J. Med. Chem. 2012, 55, 3414-3424, [3] - *ChemMedChem* 2016, *11*, 31-37, [4] - SynLett 2018, 29, A-K, [5] *Chem. Sci.* 2018, *9*, 5295-5300, [6] - *J. Med. Chem.* 2019, *62*, 1078-1095, [7] - *Org. Process Res. Dev.* 2013, *17*, 1503-1509, [8] - *Eur. J. Org. Chem.* 2000, 1137-1155, [9] - *Chem. Sci.* 2018, *9*, 5295-5300, [10] - *Eur. J. Org. Chem.* 2017, 6450-6456, [11] - *Science*, 2016, *351*, 241-246, [12] - *J. Am. Chem. Soc.* 2017, *139*, 17791-17794, [13] - *J. Med. Chem.* 2019, *62*, 1078-1095.