A new building BLOCK technique based on cycloaddition chemistry for the regiospecific linking of alicyclic sub-units as a route to large, custom-functionalised structures

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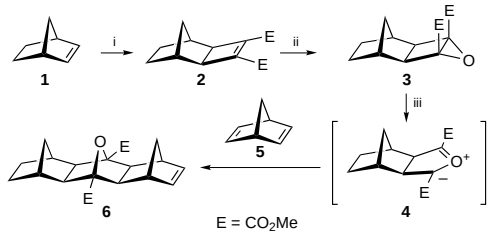
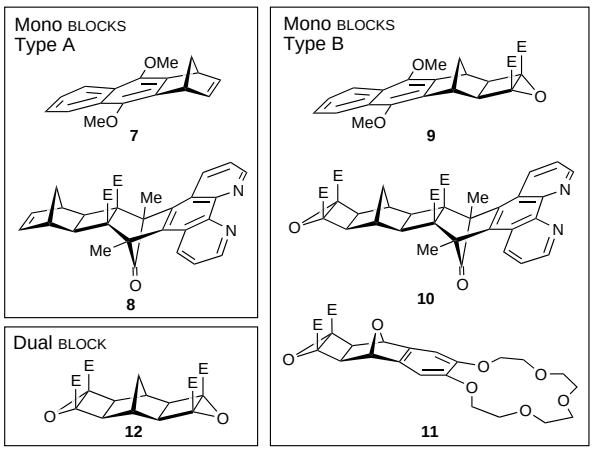
A new building BLOCK approach to synthesis has been developed where functionalised norbornenes (BLOCK A) are coupled with functionalised cyclobutene epoxides (BLOCK B) to produce A + B structures of defined geometry; use of a dual (spacer) BLOCK allows the formation of large structures where crown ether, ligand and redox centres are incorporated in similar or mixed pairings.

It is well established that there is a continuing need for the development of new substrates for supramolecular applications[1] which, in turn, requires the development of new synthetic methodology. We have recently reported the synthesis of rigid alicyclic molecules where separate donor and quencher chromophores are fused to the carbocyclic framework[2] using a serial cycloaddition technique, and this has been extended to the production of cavity-shaped crown ethers.[3] We now report a convergent method which uses preformed building BLOCKS with the particular chromophore inbuilt, and joins them thermally in a stereospecific process. The new construction technique lends itself to the production of large structures having inbuilt functional units of different types.



Scheme 1 *Reagents and conditions*: i, DMAD, $RuH_2CO(PPh_3)_3$ (*cf.* ref. 7); ii, Bu^{t}OOH, MeLi, −78 °C, 75%; iii, 110 °C, 3 h, 64%



This A + B building BLOCK method developed from our discovery that fused, ester-activated cyclobutene epoxides ring-open to 1,3-dipolar species such as **4** which can be trapped stereospecifically by ring-strained alicyclic dipolarophiles.‡ We envisaged that fused norbornenes could act as one building BLOCK and fused cyclobutene epoxides could act as the other. This was confirmed by heating norbornadiene **5** (prototype building BLOCK A) with epoxide **3**§ (prototype building BLOCK B) to produce the *exo,exo*-coupled product **6**§ (Scheme 1).¶ A + B products formed by this coupling process retain their rigid alicyclic character as the newly formed 7-oxanorbornane unit seamlessly joins the two reactants.

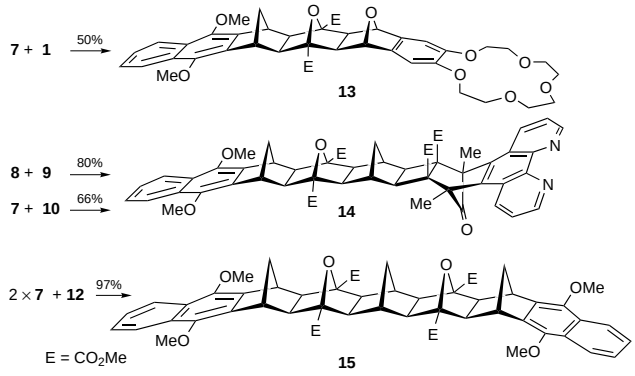
To illustrate this building block strategy further, we have assembled a small selection of functionalised molecules which form a pool of A and B reagent BLOCKS **7**–**11**. In the longer term, this pool would grow to cover other functional units and these basic A and B BLOCKS, together with the dual (spacer) BLOCK **12**, would be available in a selection of geometrical configurations (shapes). The building BLOCKS can be drawn upon in A + B pairs, depending on the type of functionality required, and heated together to form the final product. Preparation of the building BLOCKS, which are of two basic types, is made simpler as the fused norbornenes, available as the type A building BLOCK, can be converted to fused cyclobutene epoxides (type B building BLOCKS) in a two-step process involving Ru-catalysed [2 + 2] cycloaddition of dimethyl acetylenedicarboxylate (DMAD),[7] followed by epoxidation (MeLi, Bu^{t}OOH),‖ as illustrated by the conversion of **1** to **3** (Scheme 1). Simply heating BLOCK A with BLOCK B yields the coupled product in good yield and with high stereospecificity.**

While all combinations of type A plus type B BLOCKS are feasible, especially as a combinatorial exercise, only a representative set **13**–**15** (Scheme 2) is reported here. Heating the dipolarophilic norbornene **7**[8] as the type A building BLOCK containing a dimethoxynaphthalene with the cyclobutene epoxide **11** with crown ether functionality as the incipient 1,3-dipole, yielded the specifically *exo,exo*-coupled product **13** (Scheme 2). Similar A + B coupling between dipolarophile **8**[2] as the ligand carrier and epoxide **9** as the transporter for the dimethoxynaphthalene gave coupled product **14**.§ The same product **14** could be formed by the alternative A + B assembly process in which the epoxide **10** provided the ligand and norbornene **7** furnished the dimethoxynaphthalene. These routes to **14** represent new approaches to rigid polyalicyclic structures containing metal chelating centres linked with redox-active components, the first members of which were only recently reported as model systems for the study of electron and energy transfer.[2,9]

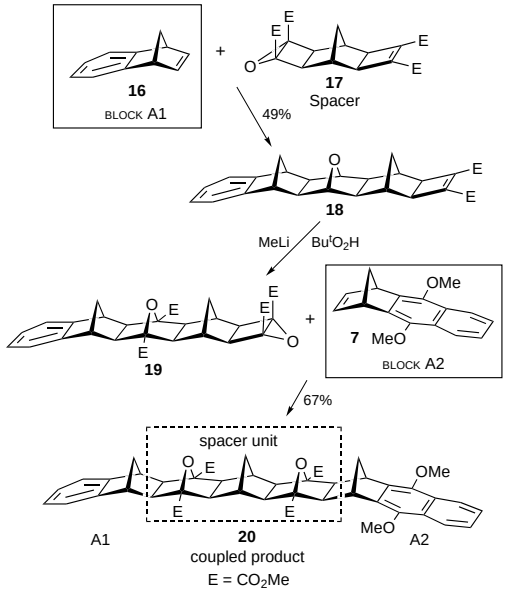
Large functionalised polynorbornanes containing two sets of the same functionality can be produced using the combination of the type A BLOCK with a dual epoxide BLOCK (Scheme 2). This approach was used to prepare the polynorbornane **15** by reaction of 2 equiv. of **7** with bis-epoxide **12**. This example illustrates special features of the methodology: (i) it provides a

mechanism for coupling reagents with functional units unstable to the epoxidation conditions, and therefore unsuitable for conversion to type B BLOCKS, by employing epoxide co-reagents; (ii) the polynorbornane framework significantly affects the geometry of the final product, especially the relative orientation of the functional unit; this can be varied by choice of the dual BLOCK.

The final example illustrates the most versatile route to large differentially functionalised structures. Treatment of spacer molecule **17**, where there is one cyclobutane epoxide (the second is latently positioned as the cyclobutene-1,2-diester), with benzonorbornadiene **16** (BLOCK Al, boxed in Scheme 3) provided the coupled product **18**, which was converted to the extended epoxide **19** by epoxidation under the usual conditions. Subsequent reaction of **19** (a standard BLOCK B) with the naphthonorbornadiene **7** (BLOCK A2, boxed in Scheme 3) furnished the large product **20** (the spacer component is designated by a dashed box in Scheme 3). Future work will involve dual BLOCKS as a carrier of separate functionality, thereby opening the way for triad formation.



Scheme 2



Scheme 3

These results establish the potential of this reaction to act as a coupling method for the construction of large polyalicyclic structures. We are developing fused norbornenes containing other important functionality, so the opportunity for building an array of bioactive products by this or related coupling methods[10,11] is well-advanced and such results will be published in due course.

Footnotes

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‡ Huisgen has reported many examples of epoxide ring-opening to 1,3-dipolar species (ref. 4), and there is one example of the thermal ring-opening of an cyclobutene epoxide with phenyl substituents on the epoxide (ref. 5), but application in the alicyclic field is new. We refer to this type of coupling as the ACE reaction, where the acronym is derived from **a**lkene plus **c**yclobutene **e**poxide coupling.

§ All new compounds gave satisfactory analytical and spectral data.

¶ Norbornene **1** reacts with **3** to produce the dihydro derivative of **6**, which is identical with that formed by an alternative route (ref. 6).

‖ Use of BuLi leads to mixtures where ester exchange products interfere.

** The success of this technique was assured when separate reaction of A or B provided no evidence for self-assembly under the coupling conditions.

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