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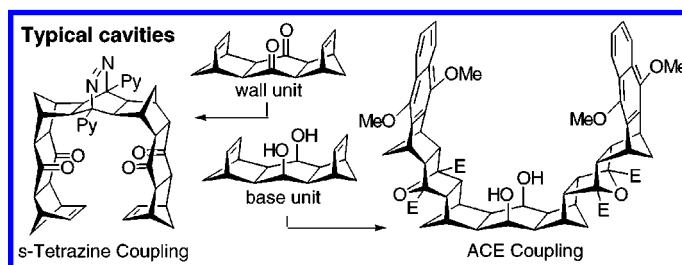
Ronald N. Warrener,^{*,†} Davor Margetic,[†] Ananda S. Amarasekara,[†]
Douglas N. Butler,[†] Indu B. Mahadevan,[‡] and Richard A. Russell[‡]

Centre for Molecular Architecture, Central Queensland University,
Rockhampton, Queensland, 4702, Australia, and Department of Biological and
Chemical Sciences, Deakin University, Geelong, Victoria, 3217, Australia

r.warrener@cqu.edu.au

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ABSTRACT



A new general route to U-type cavity structures (molecular clefts) with inside functionality has been developed using wall extension or base/roof assembly methods which draw upon (i) the 1,3-dipolar cycloaddition reaction between alkenes and cyclobutene epoxides (ACE coupling) or (ii) the Diels–Alder reaction of alkenes with fused dihydropyridazines (s-tetrazine coupling). In this way, functional units (e.g., crown ethers, redox-active naphthalenes) have been attached stereospecifically to short-walled bis-alkenes 1–5 to produce cavity structure 6–10 with top-of-wall separations (C to C) from 4.5 to 12.7 Å.

Rigid cleft molecules have been reported to act as host molecules for aromatic guests,¹ while we have reported the use of U-shaped metalated bis-porphyrins as hosts for dipyrrolyl rods in the production of a molecular universal joint.² The latter report highlights the potential of U-shaped cavity molecules to act as hosts for supramolecular applications. Although Diels–Alder and condensation routes to space-separated bifunctionalized systems have been reported, they are targeted to individual molecules³ or lack cycloaddition stereoselectivity.⁴ Since the advent of our BLOCK chemistry⁵ (Diels–Alder and 1,3-dipolar cycloadditions), we

have ways to couple reagents with high stereoselectivity, especially for reactions involving norbornenes. This background has allowed us to formulate new wall and base assembly strategies (Figure 1) for the synthesis of cavity molecules⁶ and we report our results herein. In particular, we introduce the concept of parity reversal (see definition

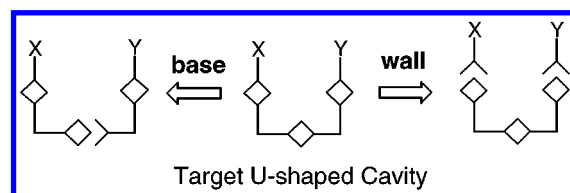


Figure 1. Cavity retrosynthesis protocols.

[†] Central Queensland University.

[‡] Deakin University.

(1) Klarner, F.-G.; Benkhoff, J.; Boese, R.; Burkert, U.; Kamieth, M.; Naatz, U. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1130–1133.

(2) Johnston, M. R.; Gunter, M. J.; Warrener, R. N. *Chem. Commun.* **1998**, 2739–2740.

(3) Atkinson, E. J.; Oliver, A. M.; Paddon-Row, M. N. *Tetrahedron Lett.* **1993**, *34*, 6147–6150.

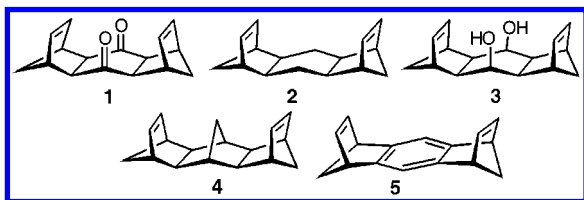


Figure 2. Base BLOCKs 1–5.

later) as an assembly protocol and demonstrate that these BLOCK methods are suitable for introducing functionality to the inner face of the cavity system.

The ability to control wall orientations takes advantage of the series of known *bis*-alkenes 1–5^{7–12} as short-walled components, where the angular relationship of the π -bonds in the terminal norbornenes changes regularly from being convergent in 1, through roughly parallel in 2 and 3 to substantially divergent in 4 and 5 (Figure 2).

While the interwall relationships are modified from those exhibited in *bis*-alkenes 1–5 when the wall is extended, owing to the changes in hybridization of the original alkene

(4) (a) Warrener, R. N.; Houghton, M. A.; Schultz, A. C.; Keene, F. R.; Kelso, L. S.; Dash, R.; Butler, D. N. *J. Chem. Soc., Chem. Commun.* **1996**, 1151–1152. (b) Warrener, R. N.; Ferreira, A. B. B.; Schultz, A. C.; Butler, D. N.; Keene, F. R.; Kelso, L. S. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 2485–2487. (c) Warrener, R. N.; Wang, S.; Russell, R. A.; Gunter, M. J. *Synlett* **1997**, 47–50.

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(6) Warrener, R. N.; Butler, D. N.; Russell, R. A. *Synlett* **1998**, 566–573.

(7) References to compounds 1–5 are 1⁸, 2⁹, 3¹⁰, 4¹¹, 5¹².

(8) Mehta, G.; Padma, S. *J. Am. Chem. Soc.* **1987**, 109, 7230–7232.

(9) Butler, D. N.; Tepperman, P. M.; Gau, R. A.; Warrener, R. N.; Watson, W. H.; Kashyap, R. P. *Tetrahedron Lett.* **1995**, 36, 6145–6148.

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(13) All compounds gave satisfactory NMR, microanalytical, or high-resolution MS data. Spectral and physical data for representative compounds are as follows. **6**, mp 270 (decomp) °C, 48% yield, ¹H NMR δ 0.90 (2H, d, J = 10 Hz); 2.20 (s, 4H); 2.26 (s, 4H); 2.50 (s, 4H); 2.63 (d, J = 10 Hz, 2H); 3.04 (s, 4H); 3.95 (s, 12H); 5.15 (s, 4H); 7.10 (m, 8H). **13**, mp 245–247 °C, 19% yield, ¹H NMR δ 0.89 (2H, d, J = 9.7 Hz); 1.32 (2H, d, J = 9.4 Hz); 1.62 (4H, s); 2.17 (4H, s); 2.31 (4H, s); 2.52 (2H, d, J = 9.7 Hz); 2.70 (2H, d, J = 9.4 Hz); 3.49 (4H, s); 3.52 (4H, s); 3.87 (12H, s); 3.91 (12H, s); 4.34 (2H, d, J = 8.4 Hz); 4.47 (2H, d, J = 8.6 Hz); 7.34–7.38 (4H, m); 7.93–7.96 (4H, m). **17**, foam, 56% yield, ¹H NMR δ 0.92 (1H, d, J = 8 Hz); 1.25 (1H, d, J = 9 Hz); 1.40 (1H, d, J = 9 Hz); 2.00 (2H, s); 2.52 (2H, s); 2.55 (1H, d, J = 8 Hz); 2.95 (2H, s); 3.34 (2H, s); 3.37 (2H, s); 3.73 (12H, m); 3.91 (2H, m); 3.94 (6H, s); 4.03 (4H, m); 5.11 (2H, s); 6.05 (2H, 6s); 6.79 (2H, s). **18**, gum, 60% yield, ¹H NMR δ 0.89 (2H, d, J = 10 Hz); 2.16 (2H, s); 2.18 (2H, s); 2.23 (4H, s); 2.49 (4H, s); 2.60 (2H, 2 x d, J = 10 Hz); 3.03 (4H, s); 3.72–3.83 (12H, m); 3.93 (6H, s); 3.94 (6H, s); 4.04 (4H, bs); 5.05 (2H, s); 5.14 (2H, s); 6.72 (2H, s); 7.10 (2H, s); 7.23 (2H, m). **20**, mp >300 °C, 52% yield, ¹H NMR δ 0.89 (2H, s); 1.33 (2H, d, J = 10.8 Hz); 1.62 (4H, br s); 1.80 (2H, d, J = 10.8 Hz); 2.07 (2H, s); 2.61 (4H, s); 2.77 (4H, s); 3.77 (12H, s). **22** mp >350 °C, 27% yield, ¹H NMR δ 0.88 (2H, d, J = 10.2 Hz); 1.12–1.56 (6H, m); 1.68 (2H, s); 2.04 (6H, s); 2.24 (4H, s); 2.32 (4H, s); 2.40 (2H, d, J = 10.2 Hz); 2.65 (2H, d, J = 9.7 Hz); 3.54 (4H, s); 3.89 (12H, s); 3.90 (12H, s); 7.34–7.38 (4H, m); 7.95–7.98 (4H, m). **25**, mp 278–279 °C, 15% yield, ¹H NMR δ 0.37 (2H, d, J = 12.1 Hz); 1.01 (4H, s); 1.28 (2H, d, J = 12.1 Hz); 1.46 (2H, s); 1.61–1.78 (8H, m); 2.05 (4H, s); 2.86 (2H, s); 3.67–4.12 (32H, m); 4.59 (4H, s); 6.60 (4H, m); 7.30–7.42 (4H, m); 7.91 (4H, dt, J = 7.5 Hz; J = 1.8 Hz); 8.75 (4H, d, J = 8.9 Hz); 8.81 (4H, td, J = 4.6 Hz, J = 1.0 Hz).

site from sp² to sp³, it is still possible to form a range of cavity geometries. This feature is illustrated by cavity systems 6–10, formed by ACE coupling of alkenes 1–5 with B-BLOCK 11, where molecular modeling results (Figure 3)

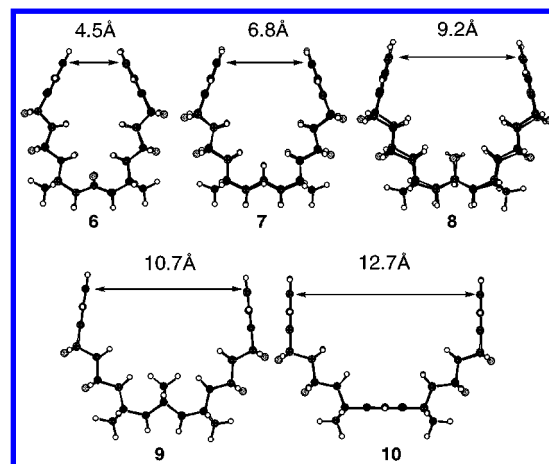
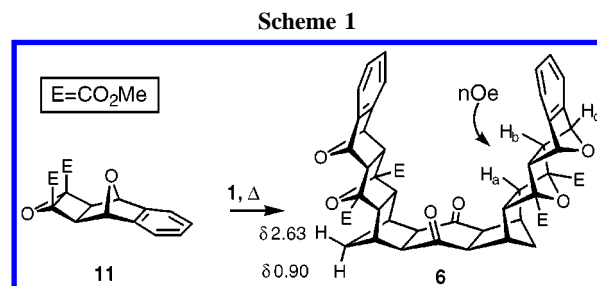


Figure 3. Inner wall distances for adducts 6–10 (AM1 optimization). Ester groups omitted from calculation.

show that the top-of-wall separation distances range 4.5–12.7 Å and that wall orientations change systematically from convergent to parallel.

Heating the *bis*-alkene 1 with the cyclobutene epoxide 11 produced the 1:2 cycloadduct 6¹³ (Scheme 1).

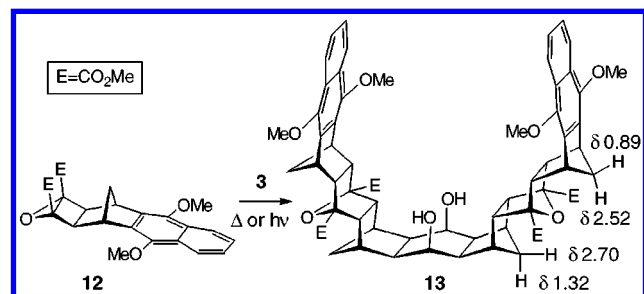


The convergent U-shaped geometry present in 6 resulted from the stereospecific *exo,exo*-coupling characteristic of the ACE-coupling procedure with norbornenes and was confirmed by ¹H NMR spectroscopy. The high symmetry of the product was typified by the single resonance of the four benzylic bridgehead protons Hc at δ 5.15 and the single resonance for the ester methyl groups (δ 3.95). The stereochemistry was fully defined by the singlet resonance for Hc which confirms its *endo*-relationship with Hb and by the presence of a *nOe* between protons Hb and Ha, which establishes their proximity as required for the proposed *exo,exo*-geometry.

The ACE methodology for cavity formation has also been applied to the *bis*-alkene 3, readily available by reduction

(LAH or NaBH₄) of dione **1**, and some new features emerge. Here, both thermal and photochemical (acetone, 300 nm) coupling between cyclobutene epoxide **12**¹³ and **3** can be achieved to yield the identical cavity product **13** (Scheme 2). Neither result is surprising in its own right, except that

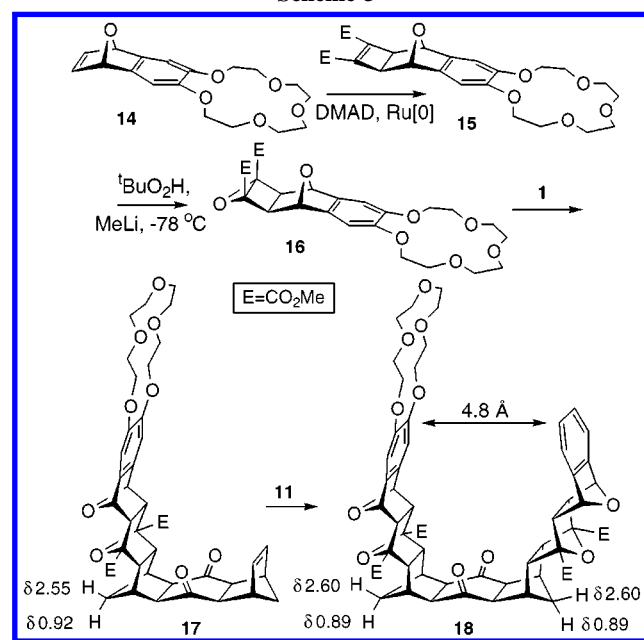
Scheme 2



substrate **3** is itself rapidly transformed photochemically to an unknown product when irradiated in acetone under the same conditions in the absence of **12**. The structure of **13** was confirmed by spectral data, inter alia, 17 x ¹³C resonances as required for the structure with C_{2v} symmetry. The stereochemistry of **13** was assigned on the basis of downfield shifts of the methylene bridge protons Ha and Hb when adjacent to the oxygen-bridge (steric compression). A similar adduct was produced by irradiation of dione **1** with cyclobutene epoxide **12**. In neither method could the reaction be made to yield 1:1 adducts.

When the cyclobutene epoxide carried additional functionality on the aromatic ring, as in the case of the crown ether **16** (for its preparation, see Scheme 3), then the cycloaddition with the convergent bis-alkene **1** stopped at the 1:1-stage producing adduct **17**.¹³

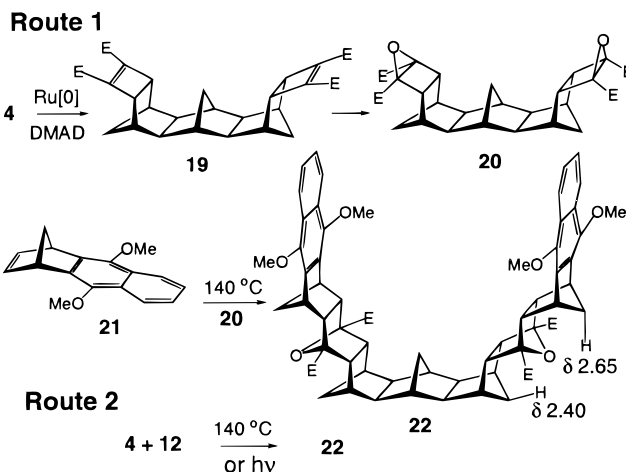
Scheme 3



Molecular modeling indicated that the crown ether portion of the 1:1 adduct **17** sterically crowds the space required by the second crown ether reagent **16** to attain the transition state for production of the cavity system. In keeping with this premise, the smaller cyclobutene epoxide **11** does yield a cycloaddition product **18** upon reaction with 1:1 adduct **17** since the incoming agent no longer encroaches on the crowded area occupied by the crown ether ring. This observation sets up the opportunity to form cavity molecules with a crown ether on one wall and a second functional unit on the other, provided, of course, that the incoming reagent is small enough to avoid the steric congestion provided by the terminal crown ether component.

The use of parity reversal where functional groups are interchanged involves a choice between which of the two BLOCKs acts as the alkene and which acts as the cyclobutene epoxide. In the examples to date, the base component has acted as the alkene and the wall extension was achieved by reaction with a functionalized cyclobutene epoxide. We tested this protocol by using a bis-epoxide base component and reacting it with an alkene wall extender. The required bis-epoxide **20**¹³ was prepared using our standard, two-step method from bis-alkene **4** (Mitsudo addition of DMAD,¹⁴ followed by nucleophilic epoxidation) (Scheme 4). Reaction

Scheme 4



of **20** with the naphthonorbornadiene **21** occurs thermally (but not photochemically) to produce **22**, identical to that formed by the other route from **4** and **12**.

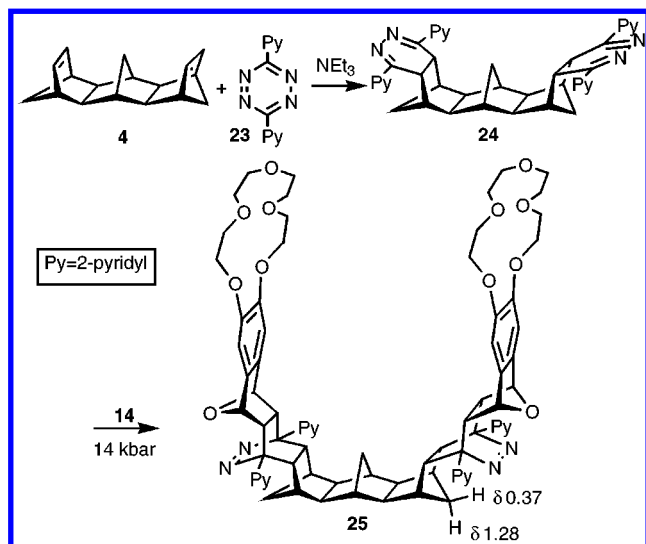
While this reverse strategy is successful with the simple norbornenes, it fails to offer a clean route to the related bis-crown-ether systems from the reaction of crown-ether A-BLOCK **14** with **20** (see the following manuscript in this issue for a solution to this problem).^{15,16} Preliminary results show that a complex mixture of products is formed and NMR analysis indicates the presence of unsymmetrical products indicative of a very rare loss of stereochemical integrity in the ACE coupling process.

(14) Mitsudo, T.; Kokuryo, K.; Shinsugi, T.; Nakagawa, Y.; Watanabe, Y.; Takegami, Y. *J. Org. Chem.* **1979**, *44*, 4492–4496.

(15) Warrenner, R. N., et al. *Org. Lett.* **1999**, *1*, 203–206.

A more profitable route to a cavity molecule with bis-crown walls was developed using the *s*-tetrazine BLOCK coupling technology (Scheme 5).¹⁶ Thus, reaction of the bis-

Scheme 5



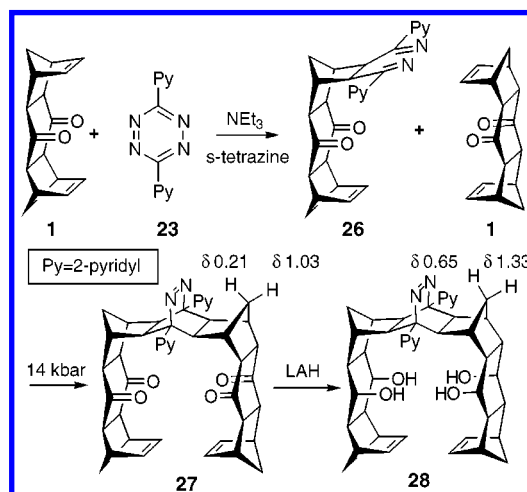
alkene **4** with 2 equiv of *s*-tetrazine **23**, in the presence of triethylamine, afforded the corresponding bis-dihydropyridazine **24** which, when reacted with the alkene BLOCK **14** under high pressure (14 kbar, CH₂Cl₂), yielded the bis-crown-ether cavity **25**.¹³

The reaction of *s*-tetrazine **23** with the dienedione **1** was much slower and stopped after the addition of only 1 equiv of *s*-tetrazine **23**, while the dienediol **3** failed to react at all. This indicates that the reactivity of the π -bonds in **1** and **3** are modified by the CO or OH substituents; indeed, we have observed earlier that alkenes **1** and **3** fail to undergo Mitsunobu addition, while the parent system **2** reacts without difficulty.¹²

Reaction of dihydropyridazine **26** in situ with alkene **1** under high pressure yielded the coupled product **27**. Although the high symmetry of the ¹H NMR spectra of **27** supported the stereochemical assignment, the proton spectrum was considerably broadened, especially in the aromatic region.

(16) Warrenner, R. N.; Margetic, D.; Russell, R. A. *Synlett* **1998**, 585–587.

Scheme 6



This broadening was removed at higher temperatures, so the phenomenon was ascribed to restricted rotation of the pyridyl substituents. The stereochemistry of the coupling step was supported by the upfield shift of one of the methylene bridge protons caused by its proximity to the azo-bridge and the attendant anisotropic shielding.

LAH reduction of the tetrone **27** yielded the tetrol **28**. The stereospecificity of this reduction step paralleled that reported earlier for the conversion of dione **1** to diol **3**.¹⁰ Again, the symmetry of the ¹H NMR spectrum of tetrol **28** was used to support the inward-facing stereochemistry assigned to the four alcohol groups.

These results firmly demonstrate that the construction of cavities with inner-face functionality is achievable by BLOCK technology, e.g., **13** and **18**, and illuminate the path to be followed if complex wall effectors are to be included in the final target molecule, e.g., crown ethers **18** and **25**. We are presently exploring the host, guest potential of these and related cavity systems, and results will be reported in due course.

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