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Synthesis of Functionalized Cavity Structures via 1,3-Dipolar Cycloaddition of Angle-Shaped Alkenes to Curved Norbornene-Framed Dipoles

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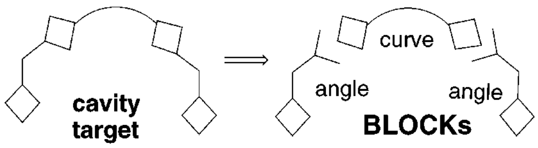
ABSTRACT



A new approach to the synthesis of cavity molecules is described in which the 1,3-dipolar ACE coupling method is used to join curved-frame spacer molecules with obtuse-angled alkenes. The curved-frame spacers are comprised of fused norbornenes in which each alternative bridge has the 7-methylene replaced by oxygen. Molecular modeling (AM1) has been used to evaluate the geometry of a selection of bis-crown ether systems, the largest of which has nine norbornane units in the frame, a separation of 20.7 Å and the walls of the cavity having an interplanar angle of 36°.

In the preceding paper in this issue,[1] we discussed the synthesis of molecular clefts via a strategy employing wall extension of upward-facing short-walled bis-alkenes. This approach demonstrated that effector groups could be incorporated into the final product using *s*-tetrazine or ACE coupling protocols. While making a significant advance in cavity molecule construction, the method was based on a "northern" extension approach (see definition at end of paper) in which the walls are upward facing relative to the norbornane frame when orientated with the methylene bridge also north facing. This motif has been the structural type used by almost all previous contributors to this field, whether using serial or convergent construction strategies, e.g., the Schiff's base methodology favored by Paddon-Row[2] and the Diels−Alder approaches used by Stoddart[3] and Klarner.[4]

Crossley[5] has described a rare example of the alternative "southern" approach, based on the use of a Tröger's base framework to form bis-porphyrin cavities. In the southern series, the wall units are downward facing relative to the normal orientation of the molecular spacer section of the frame. From a design viewpoint, the southern approach has the potential to position functionality on the underface of the norbornane frame so that it can ultimately reside on the inside of the cavity structure. In contrast, the functionality must be positioned on the upperface for inclusion in "northern" cavity systems (see Figure 3).

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[‡] Deakin University.
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(3) Ashton, P. R.; Girreser, U.; Giuffrida, D.; Kohnke, F. H.; Mathias, J. P.; Raymo, F. M.; Slawin, A. M. Z.; Stoddart, J. F.; Williams, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 5422−5429.
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In this report, we describe a new type of southern approach, which employs a curved frame as the alicyclic spacer unit to which two obtuse-angled wall components are attached using BLOCK coupling to achieve the required cavity topology (Figure 1).[6] This is a special case, as the spacer section and the walls are continuous and not readily delineated. The viability of this protocol was tested by targeting a series of bis-crown ether cavity molecules **1**−**3** and using bis-cyclobutene epoxide BLOCKs having fused norbornane frames with alkene BLOCKs in a 1,3-dipolar cycloaddition ACE coupling protocol. The alkene BLOCKs serve a dual role since they carry the effector group (crown ether in this case) and serve as the wall extender.

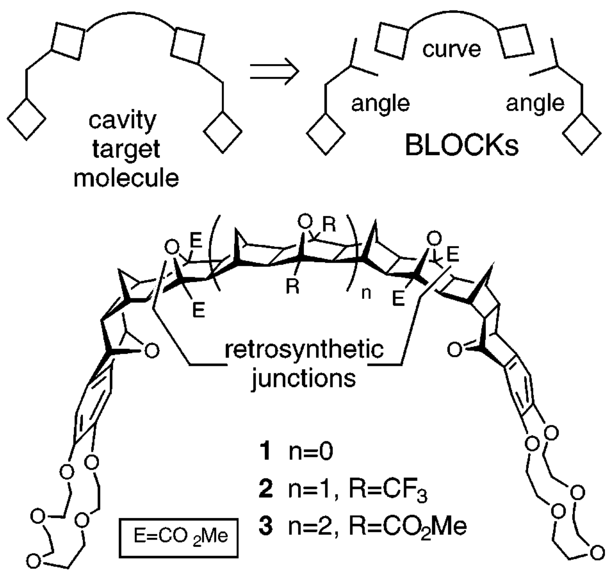


Figure 1. Retrosynthetic strategy for the construction of bis-crown ethers **1**−**3**.

Retrosynthetic analysis of target molecules **1**−**3** at the cleavage lines indicated in Figure 1, identifies a common obtuse-angled BLOCK **6** and a series of alicyclic spacers. Our analysis of this strategy commenced with the molecular modeling (AM1) of compounds **1**−**3** (molecular frames only, see Figure 2) to assess the effect that curvature in frames composed of alternatively fused norbornane and 7-oxanorbornane subunits would have on the geometry of the final product. It became apparent that the cavity walls are quite divergent when a [5]-polynorbornane module functioned as the spacer for the target molecule, e.g., **1**. Extending the frame to one having nine syn-facially fused norbornane rings (plus two others with *anti*-facial stereochemistry), e.g., **3**, significantly changes the geometry and is well on the way to producing a parallel-sided cavity system (Figure 2).

The geometry of the framework in **2** falls between that of **1** and **3**, having the interplanar angle of the aromatic rings inclined at 61°, and a separation of 18.1 Å.

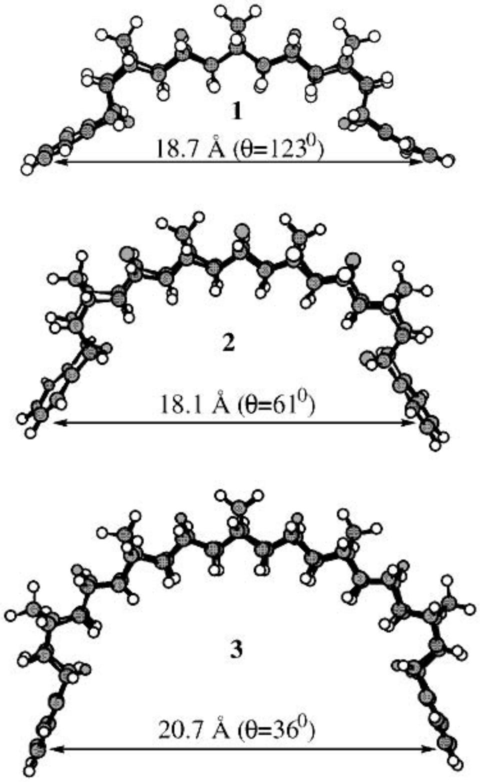
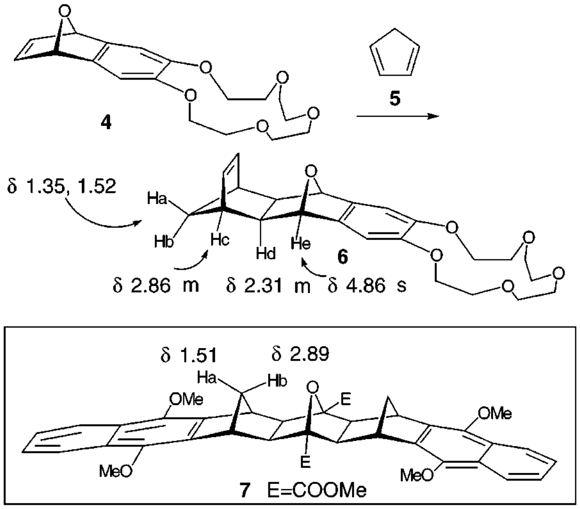


Figure 2. Molecular modeling (AM1) of the framwork components of structures **1**−**3**. The crown ether units were not included, owing to their conformational flexibility.

Formation of the common BLOCK **6** was achieved by the stereoselective addition of cyclopentadiene **5** to the known crown ether reagent **4**[7] (Scheme 1). The exo,endo stereochemistry of product **6** in this cycloaddition was critical to the overall plan, and while it had good precedent,[8] the ^{1}H NMR provided the necessary structural confirmation, since

Scheme 1



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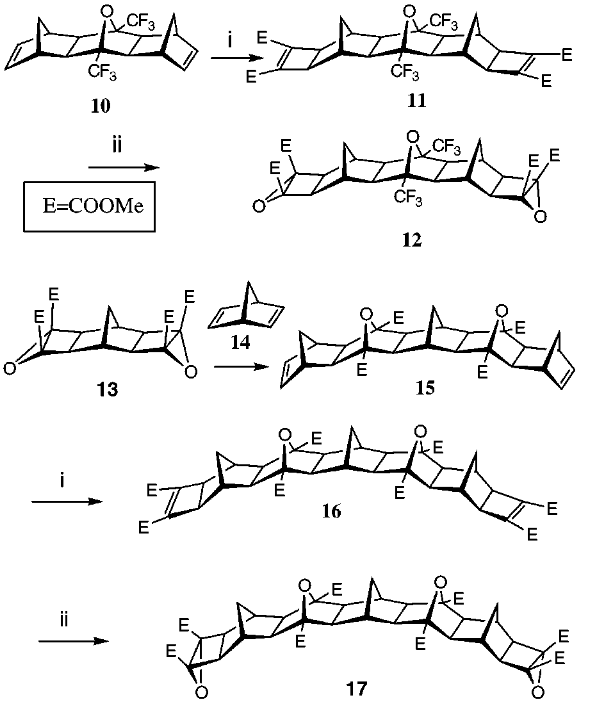
(6) Warrener, R. N.; Wang, S.; Russell, R. A. *Tetrahedron* **1997**, *53*, 3975−3990.

both the methylene bridge protons of **6** occur at a similar high field. In contrast, the methylene bridge resonances in model compound **7**, which has the alternative exo,exo stereochemistry, have the proton adjacent to the oxygen bridge shifted more than 1 ppm downfield owing to steric compression. The exact shifts of the relevant protons are annotated on the compounds structures in Scheme 1.

Formation of the new frame reagents **12** and **17** required to accompany the known bis-cyclobutene epoxide **13**[9] for these ACE coupling reactions was achieved as outlined in Scheme 2.

Scheme 2

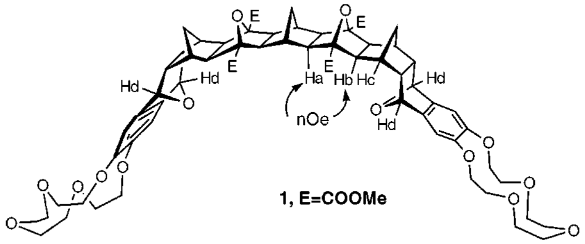


i) DMAD, $RuH_2CO(PPh_3)_3$, benzene at reflux
ii) $^tBuO_2H$, MeLi, THF, -78 °C

Subjecting hexacyclic diene **10**[10] to Mitsudo addition[11] with dimethyl acetylene dicarboxylate (DMAD) gave the bis-cyclobutene-1,2-diester **11**, which was epoxidized at low temperature to form the bis-cyclobutene epoxide **12**. The remaining reagent **17** was prepared from **13** using ACE coupling with norbornadiene **14** to produce the decacyclic diene **15**, which was subjected to the two-step process applied to the smaller diene **10** to afford the required bis-cyclobutene epoxide **17** via intermediate **16**.

Heating the obtuse-angled alkene **6** with the bis-cyclobutene epoxide **13** produced the 1:2 cycloadduct **1** (Scheme 3). The divergent geometry present in **1** resulted from the stereospecific exo,exo-coupling characteristic of the ACE-coupling procedure[9] and was confirmed by ^1H NMR spectroscopy.

Scheme 3



1, E=COOMe

$6 + 13 \longrightarrow 1$

$6 + 12 \longrightarrow 2 \qquad 6 + 17 \longrightarrow 3$

The high symmetry of the product was typified, inter alia, by the single resonance of the four benzylic bridgehead protons Hd at δ 5.05 and the single resonance for the ester methyl groups (δ 3.85). The stereochemistry was fully defined by the singlet resonance for Hb which confirms its endo relationship with Hc and the presence of a nOe between protons Ha and Hb which establishes their proximity, as required for the proposed exo,exo geometry.

Similar cycloadditions between **6** and bis-cyclobutene epoxides **12** and **17** furnished the rigidly linked crown ethers **2** and **3**. The structures of these products was again evident from the C_{2v}-symmetry displayed by each of these compounds and clearly manifested in their ^1H NMR spectra.[12]

In conclusion, the methods described herein are general and have the potential to be applied to the formation of cavity molecules carrying other effector groups. Further, a series of arc-shaped frames based on fused 7-hetero norbornanes has been developed by our group.[13] As these frames have different curvatures, this opens the way to produce related cavity systems in which the geometry of the cavity can be varied according to the particular frame employed. In this respect, the recent call for more preorganized space-separated bis-crown ether-type catalysts for ester and amide cleavage,[14] together with another pointing out the need for inside-cavity functionalization,[15] presents timely support for the type of synthetic methodology reported in this paper.

Definition of Northern and Southern Cavity Systems. In defining the types of cavity systems based on fused bicyclic rings such as norbornane, it is important to recognize that the two faces of the molecule are distinct. This manifests itself in two ways when dealing with cavity systems: (a) in the topology of the frame and its effect on the angular relationship of the walls of the cavity and (b) the ultimate positioning of frame substituents relative to the walls of the cavity. It is important, therefore, to distinguish between cavity molecules with upward-facing walls and those with downward-facing walls from both a design and construction viewpoint.

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(7) Warrener, R. N.; Wang, S.; Russell, R. A.; Gunter, M. J. *Synlett* **1997**, 47−50.

(8) We had demonstrated earlier that cyclopentadiene reacted with 7-oxanorbornenes to give exclusively the exo,endo-adduct. See Warrener, R. N.; Wang, S.; Russell, R. A. *Tetrahedron* **1997**, *53*, 3975−3990.

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(11) iMitsudo, T.; Kokuryo, K.; Shinsugi, T.; Nakagawa, Y.; Watanabe, Y.; Takegami, Y. *J. Org. Chem.* **1979**, *44*, 4492−4496.

This can be achieved using a modification of the compass coordinate system used to describe sections of complex natural products. Accordingly, we refer to compounds with upward-facing walls as northern cavity systems and those with downward facing walls as southern cavity systems (see Figure 3).

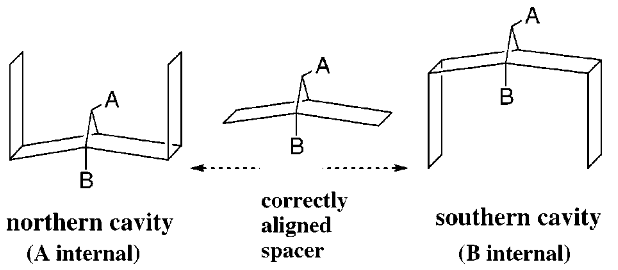

Figure 3. Diagramatic representation of "northern" and "southern" cavity molecules and the stereochemical outcome of substituents on the spacer unit.

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(12) Selected physical properties of new compounds are provided as follows: compound number, yield, mp (°C); ^{1}H and ^{13}C NMR; MS. All compods were soluble in chloroform. **1**, 34%, mp >300; ^{1}H NMR δ 0.97 (2H, d, $J = 10.2$ Hz); 1, 88 (4H, bs); 1.91 (2H, bs); 1.98 (2H, s); 2.13 (4H, s); 2.16 (4H, bs); 2.45(2H, d, $J = 10.2$ Hz); 2.51 (4H, s); 3.73 (16H, bs); 3.85 (12H, s); 3.87 (8H, m); 4.08 (4H, m); 5.05 (4H, s); 6.76 (4H, s); ESMS calcd for $C_{65}H_{76}O_{22}$, 1208.5; ESMS found, M + Na, 1231.7. **2**, 40%, mp >300; ^{1}H NMR δ 0.96 (2H, d, $J = 10.2$ Hz); 1.26 (4H, bs), 1.81 (4H, s); 1.90 (4H, s); 1.98 (4H, s); 2.04 (4H, s); 2.34 (4H, s); 2.48 (2H, d, $J = 10.2$ Hz); 2.53 (4H, s); 3.74 (16H, bs); 3.86 (12H, s); 3.98 (8H, m); 4.10 (8H, m); 5.06 (4H, s); 6.77 (4H, s). **3**, 42%, mp >300; ^{1}H NMR δ 0.96 (2H, d, $J = 10.2$ Hz); 1.25 (4H, bs), 1.45−1.58 (m, 12H); 1.76 (4H, s); 1.87 (4H, s); 1.92 (2H, s), 2.06 (4H, s); 2.16 (2H, s); 2.45 (2H, d, $J = 10.2$ Hz); 2.50 (4H, s); 3.79 (16H, bs); 3.78 (12H, s); 3.81 (12H, s); 3.89 (8H, m); 4.10 (8H, m); 5.05 (4H, s); 6.77 (4H, s); ESMS calcd for $C_{91}H_{104}O_{32}$, 1708.6; found, M + Na, 1731.6. **6** 60%, mp 140−2; ^{1}H NMR δ 1.35 (1H, d, $J = 8.1$ Hz); 1.52 (1H, d, $J = 8.1$ Hz); 2.31 (2H, bs); 2.86 (2H, bs); 3.74−4.12 (16H, m); 4.86 (2H, s); 6.08 (2H, s); 6.77 (2H, s); ^{13}C NMR δ 43.9, 49.5, 53.3, 69.6, 69.7, 70.6, 70.9. 79.8, 106.6, 133.9, 141.2, 147.3. **11**; ^{13}C NMR ($CDCl_3$) 25.39, 35.49, 45.9, 51.91, 54.32, 87.50 (q, $^{2}J_{CF} = 31.8$ Hz); 124.31 (q,$^{1}J_{CF}$ = 279.2 Hz); 141.17, 161.08; HRMS calcd for $C_{30}H_{28}O_{9}F_{6}$, 646.1637; found, 646.1643. **12**, 55% yield, mp 168−70; ^{1}H NMR δ 1.54 (2H, d, $J = 10.2$ Hz); 1.88 (4H, s); 2.00 (2H, d, $J = 10.2$ Hz); 2.19 (4H, s); 3.09 (4H, bs); 3.79 (12H, s); ^{13}C NMR ($CDCl_3$) 38.07, 49.41, 52.75, 53.81, 63.48, 87.71 (q, $^{2}J_{CF} = 32.1$ Hz), 124.23 (q, $^{1}J_{CF} = 284.4$ Hz), 164.08; HRMS calcd for $C_{30}H_{28}O_{11}F_{6}$, 678.1536; found, 678.1534. **13** (known compound[9]), 81%, mp 196−8; ^{1}H NMR 1.94 (2H, s); 2.27 (4H, s); 3.29 (2H, s); 3.83 (6H, s);^{13}C NMR ($CDCl_3$) 28.47, 36.43, 48.85, 52.43, 64.30, 164.20; HRMS calcd for $C_{19}H_{20}O_{10}$, 408.1056; found, 408.1043. **15** 72%, mp >300; ^{1}H NMR ($CDCl_3$) δ 0.98 (2H, d, $J = 8.7$ Hz); 1.93 (2H, s); 1.95 (4H, s); 2.02 (4H, s); 2.04 (4H, s); 2.32 (2H, d, $J = 8.7$ Hz); 2.62 (4H, s); 3.83 (12H, s); 6.11 (4H, s); ^{13}C NMR ($CDCl_3$) δ 28.9, 40.6, 41.8, 44.0, 52.1, 54.5, 55.7, 88.8, 139.2, 169.5; HR-ESMS calcd for $C_{33}H_{36}O_{10}$, 592.2308; found, 592.2304. **16**, 73%, mp >300; ^{1}H NMR ($CDCl_3$) δ 0.93 (2H, d, $J = 12.0$ Hz); 1.51 (4H, s); 1.91 (4H, s); 1.94 (2H, s); 1.98 (2H, s); 2.14 (4H, s); 2.16 (2H, d, $J = 12.0$ Hz); 2.55 (4H, s); 3.74 (12H, s); 3.82 (12H, s); ^{13}C NMR δ 28.2, 35. 9, 40.6, 46.0, 51.9, 52.3, 53.4, 54.9, 55.1, 89.9, 141.0, 161.2, 169.1; HR-ESMS calcd for $C_{45}H_{48}O_{18}$ + Na, 899.2738; found, 899.2710. **17**, 51% yield, mp 212−16; ^{1}H NMR 1.82 (4H, s); 1.84-(4H, s); 1.90 (4H, s); 2.10 (2H, d, $J = 9.2$ Hz); 2.18 (4H, s); 2.33 (2H, bs); 2.56 (2H, s); 2.62 (2H, d, $J = 9.2$ Hz); 3.73 (12H, s); 3.86 (12H, s); HR-ESMS calcd for $C_{59}H_{64}O_{20}$ + Na, 1115.3889; found, 1115.3875.

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