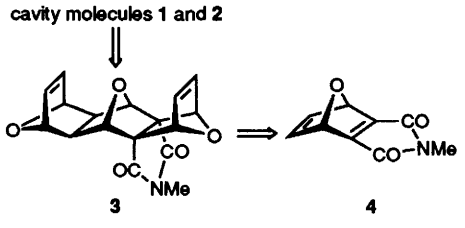
# The Synthesis of Internally Functionalised Cavity Molecules using a Cycloaddition Strategy

**Ronald N. Warrener,*[a] Ljiljana Maksimovic[a] and Douglas N. Butler[b]**

[a] *Centre for Molecular Architecture, Central Queensland University, Rockhampton, Queensland, 4702, Australia*
[b] *Chemistry Department, York University, North York, Ontario, Canada M3J 1P3*

The role of 7-oxanorbornenomaleimide **9** as an intermediate in cavity molecule construction is evaluated and other cycloaddition reactions are used to complete the sequence to **1** or **2**.

The area of host–guest chemistry continues to command special interest as chemists strive to mimic natural selectivities with unnatural molecules.[1] Cavity molecules are of special interest owing to their screened hydrophobic interiors which are enzyme-like in this regard. Molecules **1** and **2** were required as part of our programme for developing rigid cavity molecules for use in molecular recognition. Their synthesis has been approached using the retrosynthetic transform shown in Scheme 1. In this retro-cycloaddition sequence the diene **3** is identified as the common intermediate which is linked, in turn, to the 7-oxanorbornadienomaleimide **4** as starting material. This apparently trivial sequence hides the real synthetic challenge, namely the stereocontrol required in the cycloaddition reactions involved in the preparation of **3** from 7-oxanorbornadienomaleimide **4** and also those connecting **3** with target molecules **1** and **2**. We have employed furan cycloadditions onto 7-oxanorbornenomaleimides† as key steps in our approach.

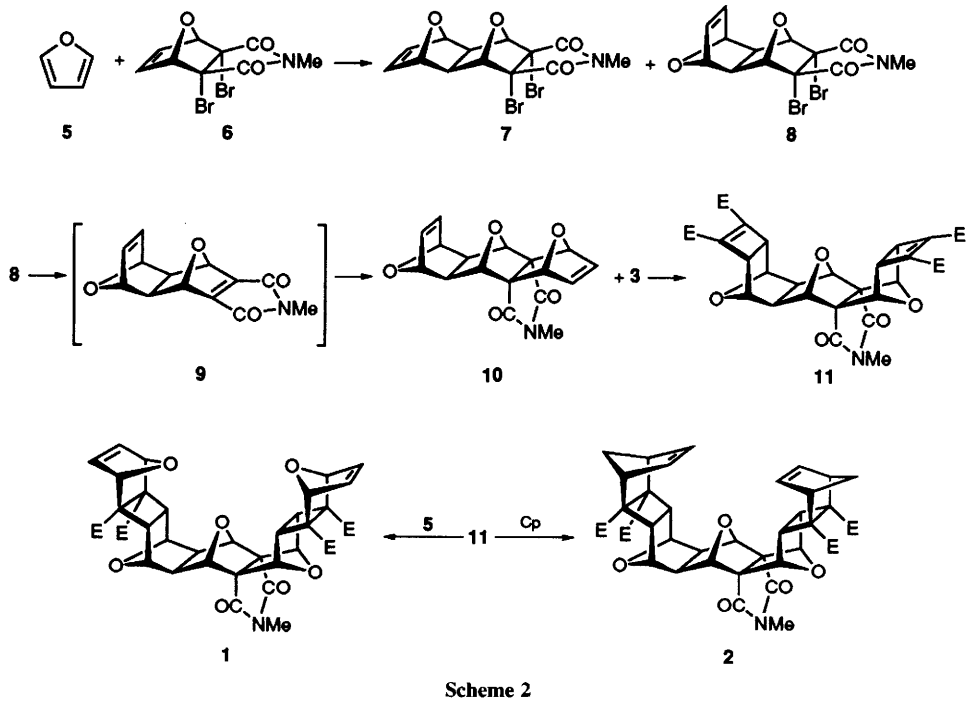



Scheme 1

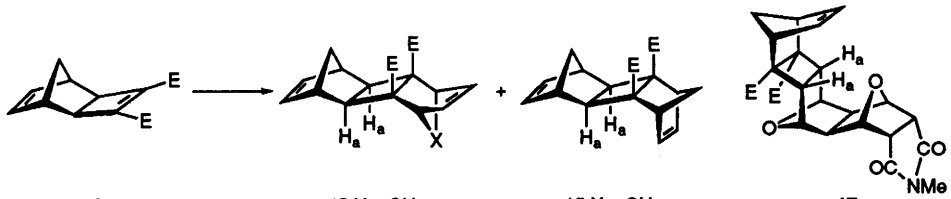
While the desired doubly bent diene can be produced, in principle, by reaction of furan with 7-oxanorbornadienomaleimide **4**,‡ we have elected to introduce the furan units without involving **4** directly. Accordingly a stepwise sequence to **3** was employed where the initial cycloaddition of furan **5** was conducted onto adduct **6**§ to produce bent adduct **8**, followed by generation and trapping of maleimide **9** with furan under mild conditions. While *N*-methyl 3,4-dibromomaleimide reacts with furan (sealed tube, 70 °C, 15 h) to yield the *exo*-succinimide **6**, it was found expedient to conduct this reaction at 85–90 °C in a sealed vessel (4 d) and produce the 2 : 1-adducts directly; isomer **8** (mp 192–194 °C) dominates 3 : 1 over **7** (mp 242–248 °C) under these conditions.¶ Addition of furan **5** to the polyalicyclic maleimide **9**, generated *in situ* by treatment of **8** with Zn/Ag couple, (THF, reflux, 30 min), yielded a 2.5 : 1 mixture of the double bent adduct **3** and the singly bent adduct **10**.‖

Thus, the doubly bent carbocycle **3** required for cavity construction (Scheme 2) was produced in two steps from readily available starting materials in 42% overall yield.

Synthesis of the penultimate product **11** was achieved by treatment of **3** with dimethyl acetylenedicarboxylate (DMAD) in the presence of $RuH_2CO(PPh_3)_3$.[5] The *exo*-selectivity of this cycloaddition is well established and the lack of coupling of the cyclobutenyl protons (δ 3.28; 3.05) in **11** is in accord with this. The final steps in the synthesis of **1** and **2** involve cycloaddition of **11** with furan and cyclopentadiene respectively. Model experiments with Smith's diester **12**[6] were used to establish the stereoselectivity of the reaction of furan with cyclobutene diesters. We have already reported that the reaction of cyclopentadiene at room temperature in diethyl




Scheme 2



12 13 X = $CH_2$ 14 X = O 15 X = $CH_2$ 16 X = O 17

ether with **12** yields adducts **13** and **15** where the *anti*-Alder cycloadduct **15** dominates (ratio 19:1).[7] Under similar thermal conditions no reaction occurred between furan and **12**, and cycloaddition could only be effected following $LiClO_4$ catalysis.[8] A single cycloadduct was produced which was assigned the Alder-stereochemistry **14** on the basis of the chemical shift (δ 1.94) of the stereochemically informative protons $H_a$ being similarly positioned with those (δ 1.76) in **13** rather than those (δ 1.34) experiencing π-bond shielding as observed in **15**.

The stereospecificity observed in these model compounds is considered to translate directly to cavity molecules **1** and **2**. Thus the bis-adduct (58%; mp 247–249 °C) derived from **11** and cyclopentadiene (Cp) is assigned the cavity structure **2** where the two olefins are inward-facing. The chemical shift of the $H_a$ protons (δ 2.05, 1.81) in **2** appeared not to support this assignment, however, reference to model compound **17** indicates that significant deshielding of the $H_a$ protons (δ 1.89) is to be expected when they are positioned within the cavity. In contrast, but in agreement with the model studies described above, the bis-adduct (86%; mp 269–271 °C) arising from cycloaddition of **5** onto **11** is assigned the outward-facing π-bond structure arising by Alder cycloaddition. The resultant cavity molecule **1** contains three oxygen bridges within the cavity with the potential to act as bonding sites. Again resonance at δ 2.41, 2.71 for the definitive $H_a$ sites in **1** show that they are well downfield of those in **2**. This supports the lack of π-bond shielding at $H_a$ as required by the Alder stereochemistry assigned to **1**.

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## Footnotes

† This approach offers an alternative to using perchlorocyclopentadiene as a synthon for cyclopentadiene to effect *endo*-selectivity onto 7-oxanorbornenes thereby avoiding the drastic reduction conditions required to remove the chlorine substituents in that process.[2]

‡ Compound **4** has been prepared by Zn/Ag debromination of **6** and reacts with furan to produce 1:1-adducts at the maleimide π-bond: *exo,exo*: *exo,endo* = 38:62.[3]

¶ The structures of **7** and **8** have been determined by X-ray crystallography (C. H. L. Kennard, unpublished results).

‖ *Selected spectroscopic data*: $^1H$ NMR data support these stereochemical assignments: **3** $^1H$ NMR (δ 6.40, 2H, t; 6.21, 2H, t; 5.13, 2H, s; 4.86, 2H, q; 4.06, 2H, s; 2.97, 3H, s; 2.55, 2H, q). **10** $^1H$ NMR (δ 6.33 2H, t; 6.10, 2H, t; 5.02, 2H, s; 4.75, 2H, q; 4.33, 2H, s; 2.65, 3H, s; 2.38, 2H, q). In particular, the *N*-methyl group is shielded (Δδ 0.32) by the π-bond in **10** relative to that in **3**.

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