The Design of Inner-Functionalised U-Shaped Cavity Molecules: Role of Phenyl Substituents at the 1,3-Position of Isobenzofurans and Oxa-Bridges in the Dienophile as Stereochemical Controlling Elements

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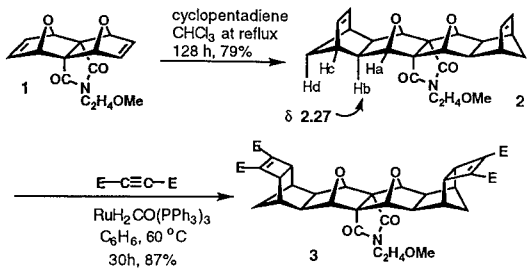
Received 18 October 1996

Abstract: 1,3-Diphenylisobenzofuran reacts with fused mono- and *bis*-norbornenes, 7-oxanorbornenes and cyclobutene-1,2-diesters with high stereospecificity whereas the corresponding isobenzofuran cycloadditions produce mixtures; this provides a basis for regulating geometry in the construction of polyalicyclic nanostructures.

The rational design of complex polyalicyclic nanostructures (PANs) depends on having reliable steps in the reaction pathway proposed for their construction. In our recent work on the synthesis of moderately large structures based on a molecular rack (molrac) framework,[1] cycloaddition reactions are strongly featured, and a knowledge of stereospecificities holds the key to obtaining the desired geometry in the final product. We and others have built upon the tandem cycloaddition strategy elaborated in our original synthesis[2] to provide excellent rigid systems for the study of energy-transfer and electron-transfer processes.[3] We have recently developed new strategies for PAN construction, especially those suitable for the preparation of U-shaped cavity molecules. This study assesses the geometrical outcome for cycloadditions involving the reaction of isobenzofurans with norbornenes, 7-oxanorbornenes and cyclobutene-1,2-diesters which are the common end-groups in polyalicyclic alkenes of the molrac type. This study serves as a model for the preparation of crown ether-functionalised nanostructures discussed in the accompanying letter where isobenzofurans are used as the delivery agent for the crown ether groups.[4]

The construction of inner-functionalised U-shaped cavity systems, where oxygen bridges serve as the potential bonding sites is one of our goals,[5] so we were particularly interested in the role such bridges might exert on the stereochemical outcomes of the cycloaddition protocol used in their construction.

The reaction of *bis*-alkene **1**[6] with cyclopentadiene occurs stereospecifically to produce the *bis*-adduct **2** in 79% isolated yield (Scheme 1), and this result is of interest in its own right. The *exo,endo*-stereochemistry of **2** is confirmed by the lack of vicinal coupling of the oxo-bridgehead proton Ha with methine proton Hb which shows that *exo*-addition has occurred onto *bis*-alkene **1** and the *endo*-fusion of the newly formed norbornene is confirmed by the presence of vicinal coupling between Hb and the methylene bridgehead proton Hc. The stereochemistry is further supported by the nOe between Hb and Hd. The mild conditions required to achieve cycloaddition (chloroform at reflux) in the one-step construction of U-shaped *bis*-alkene **2** contrast markedly with existing two-step methods required in related U-shaped *bis*-norbornene systems.[8]

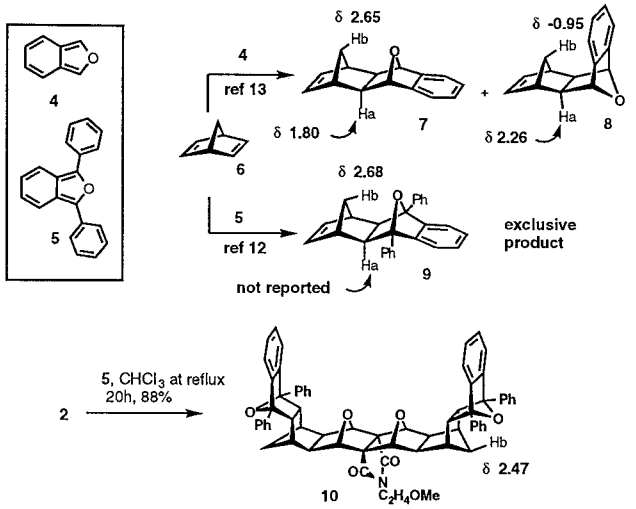


Scheme 1

In the context of U-shaped cavity production, the cyclobutene -1,2-diester **3** holds a special place as it is a highly reactive *bis*-dienophile which reacts with a range of cyclic 1,3-dienes. It was prepared by Ru-catalysed addition of dimethyl acetylenedicarboxylate onto *bis*-alkene **2**, for which there is excellent precedent to support the assigned *exo*-stereochemistry.[11]

Reaction at Norbornene π-Systems

Cava and Scheel showed some years ago that 1,3-diphenylisobenzofuran **5** formed a single stereoisomer on cycloaddition to norbornadiene **6** (Scheme 2).[12] This result contrasted with several reports where isobenzofuran **4** was stated to produce stereoisomeric adduct mixtures with norbornene or norbornadiene.[13,14] Accordingly, we first investigated the reaction of isobenzofurans **4** and **5** with *bis*-alkene **2**.



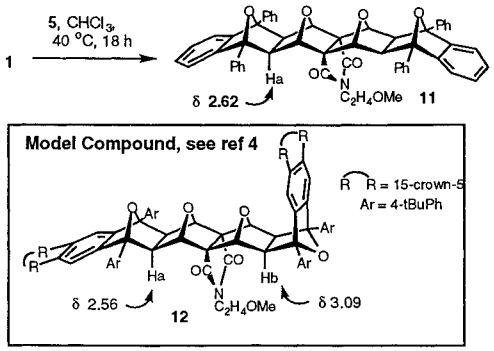
Scheme 2

Our experimental study conducted on the U-shaped *bis*-norbornene **2**, demonstrated that 1,3-diphenylisobenzofuran **5** produces the 2:1 *bis*-adduct **10** which ^{1}H NMR confirmed had C2v-symmetry. That this adduct had the same *exo,exo*-stereochemistry as that observed in norbornene was confirmed by comparing chemical shift data for the methylene bridge proton Hb in **10** with model systems **7-9** (Scheme 2).

Reaction at 7-Oxanorbornene π-Systems

The earlier report indicated that reaction of isobenzofuran **4** with a *bis*(7-oxanorbornene) related to **1**, in which the succinimide ring has been replaced by two ester groups, produced all three isomers with the U-shaped *bis*-adduct dominant (50%).[7] This type of cycloaddition can be made specific in the case of *bis*-alkene **1** by using 1,3-diphenylisobenzofuran **5** which provides the extended *bis*-adduct **11** exclusively. Justification for the *exo,exo*-stereochemistry assigned to **11** rests on chemical shift data where protons Ha (δ 2.62) must be used as the probe. We caution that stereochemical assignments based on chemical shift data alone can be problematic unless appropriate model compounds are used as references. Such protons occur at higher field in related *exo,exo*-structures as illustrated by the chemical shift data for **7** (δ 1.80)[13] relative to *exo,endo*-structure **8** (δ 2.26)[13] (Scheme 2); significantly, in this case, NMR data for **9** was not reported,[12] and in its absence it would seem logical to assign the bent *exo,endo*-stereochemistry to *bis*-adduct **11**.

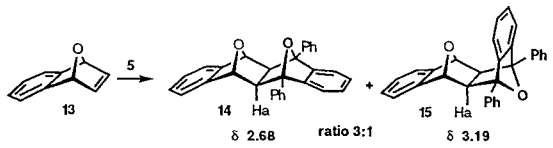
Fortunately, other data are available in the accompanying letter[4] for the unsymmetrical 2:1 adduct **12** which supports the alternative *exo,exo*-stereochemical assignment (Scheme 3). The adduct **12** contains both type of stereochemical fusion, and the definitive Ha protons occur at δ 2.56 in the extended section and δ 3.09 in the bent section. The anisotropy of the bridgehead aryl substituents accounts for the differences in chemical shifts



Scheme 3

between the two sets of models: these *deshield* the Ha protons by around 0.5 ppm and this accounts for the fortuitous similarity of proton shift data for Ha protons in the extended isomers in the aryl series and the Ha protons of the bent isomers in the parent series.

The benzo-7-oxanorbornadiene **13** has been used as a substrate for isobenzofuran cycloaddition where reaction with isobenzofuran **4** was shown by Fieser to give preferentially the *exo,endo*-isomer (ratio 7:5), whereas 1,3-dimethylisobenzofuran yields the *exo,exo*-isomer as its favourite (ratio 5:3).[15] In the current context, 7-oxanorbornadiene **13** was reacted with 1,3-diphenylisobenzofuran **5** to produce a 3:1 ratio of products **14** and **15** (Scheme 4). Chemical shift data for Ha was used as the stereochemical probe and having data for both isomers makes this method more reliable. This example appears to be one of the rare instances where **5** does not give a single stereoisomer. These results, however, do show a trend where increasing the steric bulk of the 1,3-substituents of the isobenzofuran Ph>Me>H increases the proportion of the *exo,exo*-isomer and this should prove useful in design.

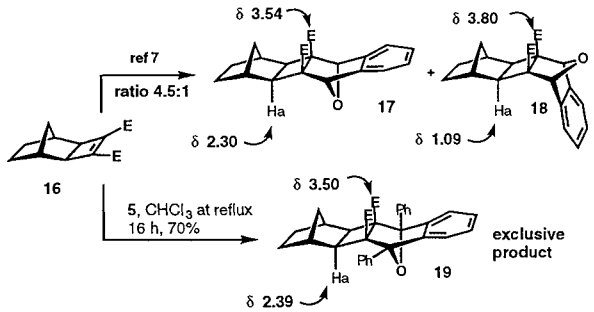


Scheme 4

Reaction at Cyclobutene-1,2-Diester π-Systems

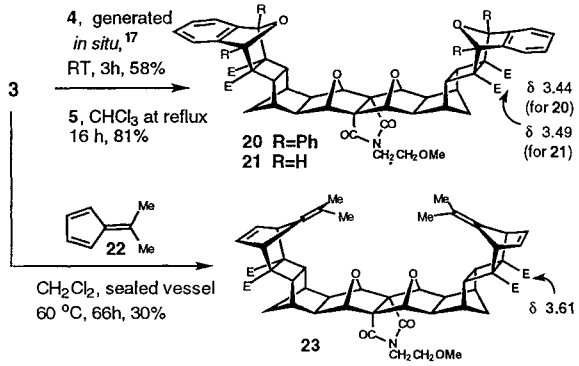
We had reported earlier that isobenzofuran **4** reacted with the simple cyclobutene **16** to furnish a 4.5:1 ratio of the extended isomer **17** and bent isomer **18** (Scheme 5).[4]

We now show that this stereo-preference can be reinforced by using 1,3-diphenylisobenzofuran **5** which produces the extended isomer **19** exclusively. The stereochemistry assigned to **19** is based on the similarity of the chemical shift for Ha in **19** (δ 2.39) and **17** (δ 2.30), but not **18** (δ 1.09), as listed in Scheme 5. In this case the chemical shift of the ester groups provides a second marker and here the assignment is reinforced (see figures in Scheme 5).



Scheme 5

In the context of U-shaped cavity production, the *bis*-(cyclobutene-1,2-diester) **3** was reacted with 1,3-diphenyl isobenzofuran **5** to produce the *bis*-adduct **20** confirming the expected stereospecificity of this reaction (Scheme 6). Substrate **3** produces only the extended product **21** when treated with isobenzofuran **4**. Substrate **3** also reacts with several other cyclic dienes to produce the extended isomers, eg, 6,6-dimethylfulvene **22** forms *bis*-adduct **23** exclusively. Thus methods are available to introduce further oxygens on the inner face of the U-shaped cavity *via* isobenzofurans (or furan)[16] and similarly positioned isopropylidene groups *via* fulvene cycloadditions. Cyclopentadienones also react with the same stereospecificity with **3**, so carbonyl groups can be introduced as inward-facing substituents.



Scheme 6

In conclusion, it has been shown that 7-oxanorbornenes and their norbornenes counterparts provide similar geometrical outcomes in PAN construction. The use of phenyl substituents to control stereochemistry in isobenzofuran cycloadditions has opened the way for their use as quality delivery agents in PAN synthesis.

Acknowledgements. R.N.W. acknowledges the award of a senior ARC Fellowship (1992-1996). S.W. thanks the Centre for Molecular Architecture for provision of a PhD Scholarship. Funding from the Australian Research Council and Central Queensland University supported this research.

References and notes

(1) Butler, D. N.; Smits, R.; Evans, D. A. C.; Weerasuria, K. D. V.; Warrener, R. N. *Tetrahedron Lett.* **1996**, *37*, 2157. Warrener, R. N.; Maksimovic, L.; Pitt, I. G.; Mahadevan, I.; Russell, R. A.; Tiekink, E. R. T. *Tetrahedron Lett.* **1996**, *37*, 3773. Butler, D. N.; Tepperman, P. M.; Gau, R. A.; Warrener, R. N.*Tetrahedron Lett.* **1996**, *37*, 2825-2828. Warrener, R. N.; Wang, S.; Maksimovic, L.; Tepperman, P. M.; Butler, D. N. *Tetrahedron Lett.* **1995**, *36*, 6141. Warrener, R. N.; Elsey, G. M.; Houghton, M. A. *J. Chem. Soc. Chem. Commun.* **1995**, 1417. Warrener, R. N.; Abbenante, G.; Solomon, R. G.; Russell, R. A. *Tetrahedron Lett.* **1994**, *35*, 7639. Warrener, R. N.; Abbenante, G.; Kennard, C. H. L. *J. Am. Chem. Soc.* **1994**, *116*, 3645. Warrener, R. N.; Pitt, I. G.; Nunn, E. E. *Tetrahedron Lett.* **1994**, *35*, 621. Warrener, R. N. *Chem. Aust.* **1992**, *59*, 578. Warrener, R. N.; Groundwater, P.; Pitt, I. G.; Butler, D. N.; Russell, R. A. *Tetrahedron Lett.* **1991**, *32*, 1885. Warrener, R. N.; Evans, D. A.; Russell, R. A. *ibid.* **1984**, *25*, 4833. Butler, D. N.; Tepperman, P. M.; Gau, R. A.; Warrener, R. N.; Watson, W. H.; Kashyap, R. P. *ibid.* **1995**, *36*, 6145.

(2) Warrener, R. N.; Pitt, I. G.; Butler, D. N. *J. Chem. Soc., Chem. Commun.* **1983**, 1340.

(3) Klarner, F.-G.; Benkhoff, J.; Boese, R.; Burkert, U.; Kamieth, M.; Naatz, U. *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 1130. Benkhoff, J.; Boese, R.; Klarner, F.-G.; Wigger, A. E. *Tetrahedron Lett.* **1994**, *35*, 73. Kumar, K.; Tepper, R. J.; Zeng, Y.; Zimmt, M. B. *J. Org. Chem.* **1995**, *60*, 4051 and references therein; Ashton, P. R. *et al., J. Am. Chem. Soc.* **1992**, *114*, 6330. *ibid.* **1993**, *115*, 5422. Mathias, J. P.; Stoddart, J. F. *Chem. Soc. Rev.* **1992**, *21*, 215. Ashton, P. R.; Mathias, J. P.; Stoddart, J. F. *Synthesis* **1993**, 221. Lawson, J. M.; Oliver, A. M.; Rothenfluh, D. F.; An, Y.-Z.; Ellis, G. A.; Ranasinghe, M. G.; Khan, S. I.; Franz, A. G.; Ganapathi, P. S.; Shephard, M. J.; Paddon-Row, M. N.; Rubin, Y. *J. Org. Chem.* **1996**, *61*, 5032, and references cited therein.

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

(5) Warrener, R. N.; Maksimovic, L.; Elsey, G. M.; Butler, D. N. *J. Chem. Soc., Chem. Commun.*, **1994**, 1831.

(6) Imide **1** is prepared from the corresponding anhydride[7] by reaction with the 2-methoxyethylamine in chloroform at reflux (4 days), followed by cyclisation of the resulting amic acid with $NaOAc/Ac_2O$.

Data for **1** and related new structures reported in this letter, follow:

1 (60 %), m.p. 221-222 °C. ^1H NMR ($CDCl_3$) δ: 3.28 (3H, s), 3.34 (2H, m), 3.42 (2H, m), 5.24 (4H, sbr), 6.58 (4H, m); ^{13}C NMR ($CDCl_3$) δ 37.74, 58.36, 68.41, 69.29, 81.30, 138.95, 174.12.

2 (79 %), m.p. 169-170 °C; ^1H NMR ($CDCl_3$) δ 0.98 (2H, d, *J* = 8.1 Hz), 1.12 (2H, m), 2.27 (4H, m), 2.82 (4H, m), 3.26 (3H, s), 3.54 (2H, m), 3.63 (2H, s), 4.31 (4H, s), 5.81 (4H, t, *J* = 3.42 Hz, 1.71 Hz); ^{13}C NMR ($CDCl_3$) δ 37.70, 45.15, 46.39, 50.39, 58.30, 68.18, 73.46, 81.37, 133.25, 174.98.

3 (87 %), m.p. 278 °C (dec.). ^1H NMR ($CDCl_3$) δ 0.95 (2H, d, *J* = 10.9 Hz), 1.42 (2H, d, *J* = 10.9 Hz), 2.19 (4H, dd, *J* = 2.8 Hz), 2.43 (4H, sbr), 2.95 (4H, s), 3.28 (3 H, s), 3.55 (2H, m), 3.62 (2H, m), 3.74 (12H, s), 4.74 (4H, s); ^{13}C NMR ($CDCl_3$) δ 32.44, 36.79, 38.07, 42.96, 46.35, 51.76, 58.54, 68.28, 71.68, 81.26, 141.29, 161.33, 174.50.

10 (88 %), m.p. 285-286 °C; ^1H NMR ($CDCl_3$) δ 0.51 (2H, d, *J* = 9.8 Hz), 1.91 (4H, br), 2.15 (4H, br), 2.47 (2H, d, *J* = 9.8 Hz), 2.50 (4H, s), 3.10 (3H, s), 3.36 (2H, m), 3.46 (2H, m), 4.59 (4H, s), 6.99-7.60 (28H, m). ^{13}C NMR ($CDCl_3$) δ 35.87, 38.03, 41.05, 47.70, 50.30, 58.46, 68.27, 72.26, 81.39, 90.07, 117.87, 125.84, 126.34, 127.15, 128.39, 137.59, 148.89, 174.42.

19 (70%), m.p. 153-154 °C. ^1H NMR ($CDCl_3$) δ 0.96 (2H, m), 1.30 (1H, d, *J* = 5.5 Hz), 1.46 (2H, m), 2.24 (1H, d, *J* = 5.5 Hz), 2.39 (2H, s), 2.52 (2H, br), 3.50 (6H, s), 7.03-7.63 (14H, m).

20 (81 %), m.p. 154-156 °C; ^1H NMR ($CDCl_3$) δ 1.16 (2H, d, *J* = 11.4 Hz), 2.01 (4H, m), 2.18 (2H, d, *J* =11.4 Hz), 2.62 (8H, s), 3.26 (3H, s), 3.44 (12H, s), 3.50 (4H, m), 4.34 (4H, s), 7.00-7.55 (28H, m). ^{13}C NMR ($CDCl_3$) δ 37.93, 38.64, 40.79, 47.76, 50.78, 50.82, 58.57, 64.91, 68.32, 72.58, 80.72 , 92.19, 121.56, 126.21, 127.81, 127.99, 128.52, 134.91, 146.71, 169.60, 175.04.

21 (58%), m.p. 314-316 °C; ^1H NMR ($CDCl_3$) δ 1.05 (2H, d, *J* = 9.2 Hz), 2.14 (4H, br), 2.17 (2H, d, *J* = 9.2 Hz), 2.42 (4H, br), 2.56 (4H, s), 3.24 (3H, s), 3.49 (12H, s), 3.56 (4H, m), 4.72 (4H, s), 5.17 (4H, s), 7.12 (8H, br).

23 (30%), m.p. 152-154 °C; ^1H NMR ($CDCl_3$) δ 1.03 (2H, d, *J* = 10.5 Hz), 1.64 (12H, s), 1.91 (4H, s), 2.01 (4H, m), 2.05 (2H, d, *J* = 10.5 Hz), 2.41 (4H, sbr), 3.26 (3H, s), 3.46 (4H, t, *J* = 1.8 Hz, 3.7 Hz), 3.48-3.56 (4H, m), 3.61 (12H, s), 4.42 (4H, s), 6.23 (4H, t, *J* = 1.8 Hz, 3.7 Hz). ^{13}C NMR ($CDCl_3$) δ 19.88, 37.18, 38.03, 40.38, 43.86, 46.97, 51.13, 52.88, 58.65, 59.16, 68.41, 72.16, 81.27, 114.96, 135.14, 142.11, 171.48, 174.90.

(7) Warrener, R. N.; Butler, D. N.; Liao, W. Y.; Pitt, I. G.; Russell, R. A.; *Tetrahedron Lett.* **1991** *32*, 1889.

(8) Typically, cycloaddition with hexachlorocyclopentadiene at 140 °C is used to achieve formation of an adduct with the required *exo,endo-* stereochemistry, and this is followed by strong reduction conditions (Na in ROH) to remove the unwanted Cl-substituents.[9,10]

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

(10) Paddon-Row, M. N.; Cotsaris, E.; Patney, H. K. *Tetrahedron* **1986**, *41*, 1729.

(11) Mitsudo, T.; Naruse, H.; Kondo, T.; Ozaki, Y.; Watanabe, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 580. Mitsudo, T.; Kokuryo, K.; Shinsugi, T.; Nakagawa, Y.; Watanabe, Y.; Takegami, Y. *J. Org. Chem.* **1979**, *44*, 4492. Warrener, R. N.; Pitt, I. G.; Butler, D. N. *J. Chem. Soc., Chem. Commun.* **1983**, 1340.

(12) Cava, M. P.; Scheel, F. M. *J. Org. Chem.* **1967**, *32*, 1304.

(13) Jones, D. W.; Kneen, G. *J. Chem. Soc., Perkin Trans I* **1976**, 1647.

(14) Makhlouf, M. A.; Rickborn, B.; *J. Org. Chem.* **1981**, *46*, 2734.

(15) Fieser, L. F.; Haddadin, M. J. *Can. J. Chem.* **1965**, *43*, 1599

(16) Furan cycloadditions could also achieve this result, however while furan can be made to react with **10** under high pressure, the product has only limited stability, rapidly fragmenting back to starting materials at ambient temperature and pressure.

(17) Warrener, R. N. *J. Am. Chem. Soc.* **1971**, *93*, 2346.