Pure & Appl. Chem., Vol. 61, No. 9, pp. 1581–1586, 1989.
Printed in Great Britain.

The evolution of molecular belts and collars

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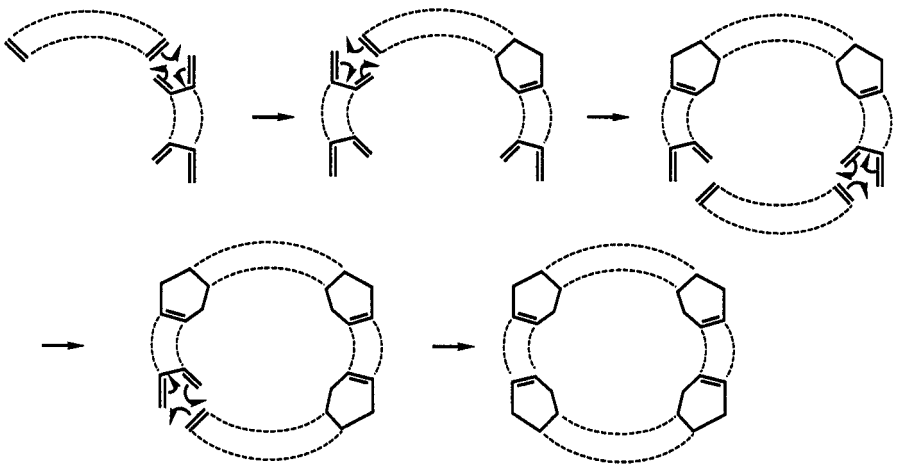
Abstract – The Diels-Alder reaction has been employed to synthesise a hexaepoxyoctacosahydro[12]cyclacene derivative **6** in a highly efficient manner from the *syn*-isomer **1** of 1,4:5,8-diepoxy-1,4,5,8-tetrahydroanthracene and 2,3,5,6-tetramethylene-7-oxabicyclo[2.2.1]heptane **2**. Each time a new cyclohexene ring is formed in the macropolycyclisation process, which utilises two molar equivalents of both the bisdienophile **1** and the bisdiene **2**, the cycloadditions are trebly diastereoselective. A sequence of reactions on compound **6** involving (i) deoxygenation, (ii) dehydration, and (iii) partial hydrogenation have led to the isolation and characterisation of the D_{6h} symmetrical dodecahydro[12]cyclacene derivative **10** containing six benzene rings. The synthetic strategy is new and the macropolycyclic compounds, which can be prepared according to this kind of molecular 'LEGO', are novel.

INTRODUCTION

Many macrocycles with molecular receptor properties have been made in recent years. With a few notable exceptions[1], most of the synthetic molecular receptors of well-defined shapes with rigid cavities emerge after highly elaborate syntheses. In a search for new and efficient synthetic procedures for the preparation of rigid collar-like molecules, which would offer a lot of flexibility in terms of (i) structure, (ii) size, (iii) shape, (iv) electronic characteristics, (v) functionality, and (vi) properties, we have identified the Diels-Alder reaction[2] as a route to a novel range of macropolycycles composed of laterally-fused six-membered rings. This well-known reaction, which has been much used, particularly in the synthesis of natural products, has a number of attractive features. It (i) can involve cheap and readily-available starting materials, (ii) affords six-membered rings by a mechanism in which two bonds are formed more or less simultaneously, (iii) usually proceeds in very high yields, and (iv) requires no reagents, a fact which assists greatly in product isolation. If necessary, it can be (i) performed in a range of solvents including water, (ii) carried out over a wide temperature range, (iii) promoted by very high pressures, and (iv) catalysed by Lewis acids. Moreover, the reaction mechanism is well-understood. It exhibits (i) high regioselectivity, (ii) complete stereospecificity (*cis*-addition), and (iii) high stereoselectivity, *e.g. endo* and *exo* configurational control with respect to bicyclic systems. It is quite remarkable that, with all these attributes, the Diels-Alder reaction has not been employed previously, at least to our knowledge, in the synthesis of macropolycyclic compounds. The synthetic strategy is based on the idea (Scheme 1) that suitable bisdienes and bisdienophiles should be able to undergo repetitive cycloadditions until the 'head bites the tail' of a growing polymer strip in a final intramolecular Diels-Alder reaction to afford a macropolycycle. The challenge resides in identifying both a bisdienophile and a bisdiene with rigid structures, the 'correct' conformations, and the appropriate stereoelectronic characteristics to demonstrate that the strategy is sound and does work.

Scheme 1

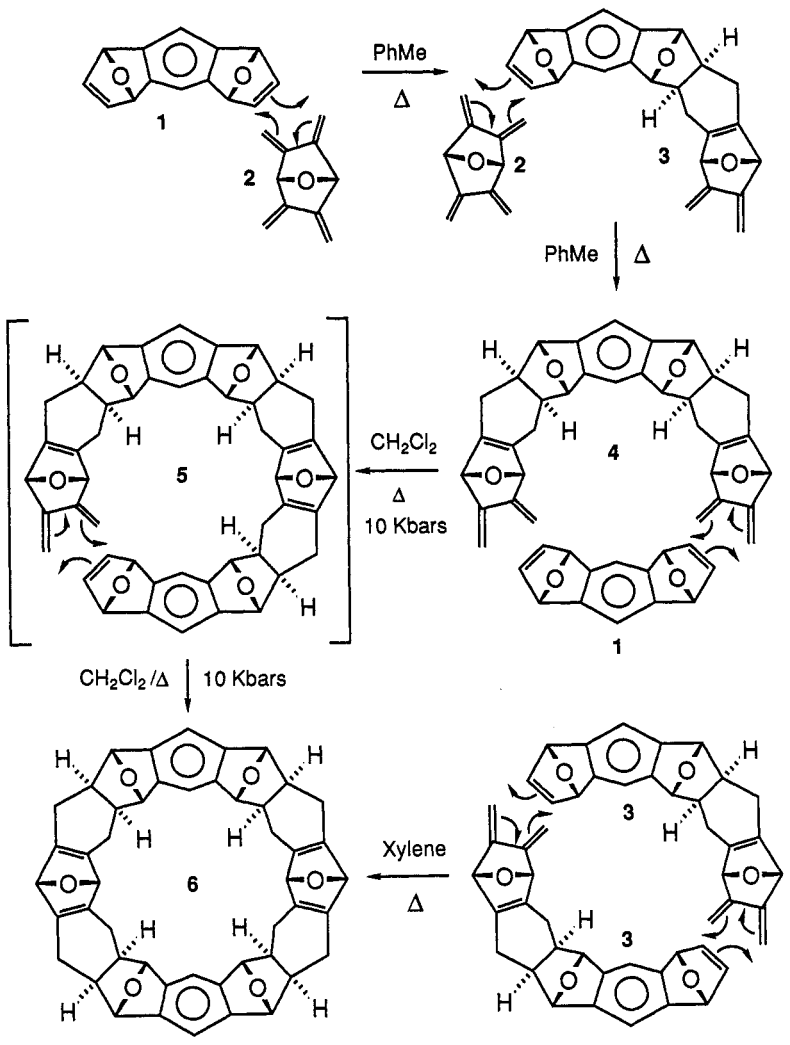


A general strategy for molecular belt formation as a result of repetitive Diels-Alder reactions between two bisdiene units and two bisdienophilic units

MOLECULAR 'LEGO'

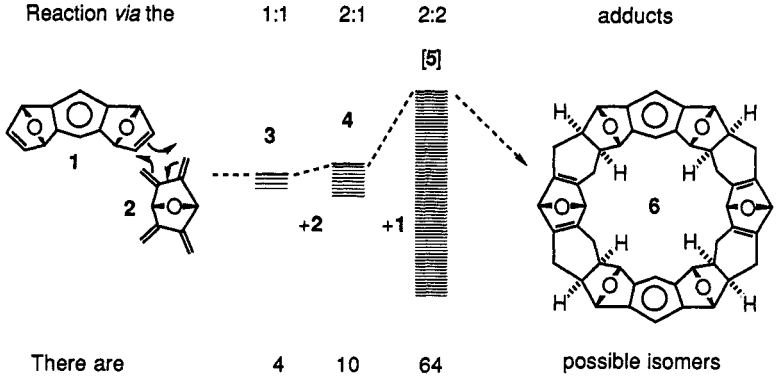
Recently, we described[3] the making (Scheme 2) of the molecular belt compound **6**, a possible precursor[4] of [12]beltene[5] starting from the known[6,7] bisdienophile **1** and bisdiene **2**. There is much evidence in the literature[8] for the highly diastereoselective attacks (i) by dienes at the *exo*-faces of dienophilic units such as those present in **1** and (ii) by dienophiles at the *endo*-faces of diene units such as those present in **2**. The success of the Diels-Alder approach to making macropolycycles is a direct consequence of the treble diastereoselectivity expressed (Scheme 3) every time a new cyclohexene ring is formed in repetitive cycloadditions. For example, there are another 9 diastereoisomeric forms of **4**, yet the 2:1 adduct has been isolated in 78% yield from a reaction of **1** with an excess of **2**: the other major product from this first reaction in refluxing toluene is the 1:1 adduct **3** of which there are another 3 diastereoisomers. There is a good reason why this particular 2:1 adduct, *i.e.* **4**, accumulates during the reaction: it is because the bisdiene **2** forms monoadducts *ca.* 100 times faster than it forms bisadducts.[7] The 1:1 adduct **3** can be converted (Scheme 2) into the macrocycle **6** – a 3.5% yield has been obtained from the cyclodimerisation of **3** in refluxing xylene. However, by far the most efficient way to obtain **6** is to subject molar equivalents of the 2:1 adduct **4** and the bisdienophile **1** to very high pressure (10 kbars) in dichloromethane solution at 60°C: in this manner, the yield of the macropolycycle **6** has been raised to 36% in this final step where **5** is presumably the intermediate that precedes the final intramolecular cycloaddition step (Scheme 2). Obviously, strong stereoelectronic effects are operating at each cycloaddition step. In accordance with literature precedent,[8] the bond-forming approaches to the dienophilic components of **1** and the diene components of **2** appear to be exclusively (Scheme 4) *exo* and *endo*, respectively. On account of the 4 'close' (*exo*-1, *endo*-1, *exo*-2, and *endo*-2) and 2 'remote' (*syn* and *anti*) configurational possibilities, there are 8 different ways (*i.e.* there is a two-fold degeneracy) for **1** to react with **2** to give 4 diastereoisomeric 1:1 adducts including **3** with the *syn/endo*-H configuration, which is the only one isolated. The other 3 diastereoisomers **3a**, **3b**, and **3c** which have, respectively, the *syn/exo*-H, *anti/endo*-H, and *anti/exo*-H configurations have not been detected so far. Inspection of molecular models (in the hands or on the computer) demonstrate that the stereoelectronic requirements for the 'close' stereochemistry dictate that the 'remote' stereochemistry must be *syn*. For steric reasons, *anti* stereochemistry is 'impossible'. And so, steric and stereoelectronic reasons combine[9] to impose

Scheme 2



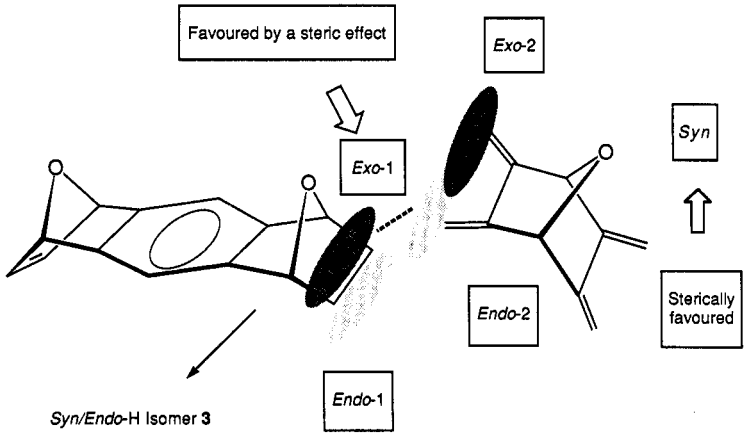
The making of the molecular belt compound **6** by a stereoelectronically-programmed set of Diels-Alder reactions starting from the bisdienophile **1** and the bisdiene **2**. The way the bicyclic ring systems have been drawn, front and back approaches to the reacting π-systems correspond to *exo* and *endo* attacks, respectively.

Scheme 3



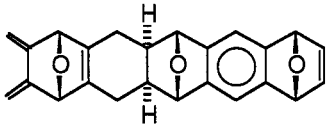
The evolutionary synthetic pathway traced by the reaction of the bisdienophile **1** with the bisdiene **2** on their way to the macropolycycle **6**.

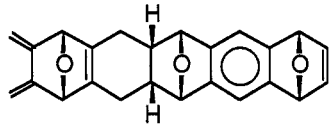
Scheme 4

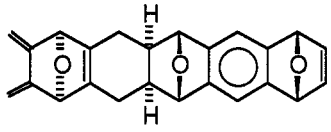


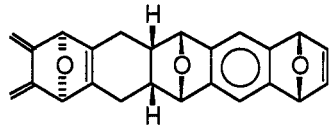
The bisdienophile **1** and bisdiene **2** showing the *exo* and *endo* faces of the reactive components and a rationalisation for the favoured *syn/exo*-1/*endo*-2 transition state leading to the 1:1 adduct **3** with *syn/endo*-H stereochemistry.

treble diastereoselectivity *via* a *syn/exo*-1/*endo*-2 transition state. This act is repeated in a further 3 Diels-Alder reactions to produce the macropolycycle **6** with its 16 chiral centres. It would seem that the stereoelectronic features of **1** and **2** are ultimately expressed in **6** in almost evolutionary fashion. No reagent control is required. We believe we have discovered a stereoelectronically-controlled molecular 'LEGO' set.[9]


Syn/Endo-H Isomer **3**


Syn/Exo-H Isomer **3a**


Anti/Endo-H Isomer **3b**


Anti/Exo-H Isomer **3c**

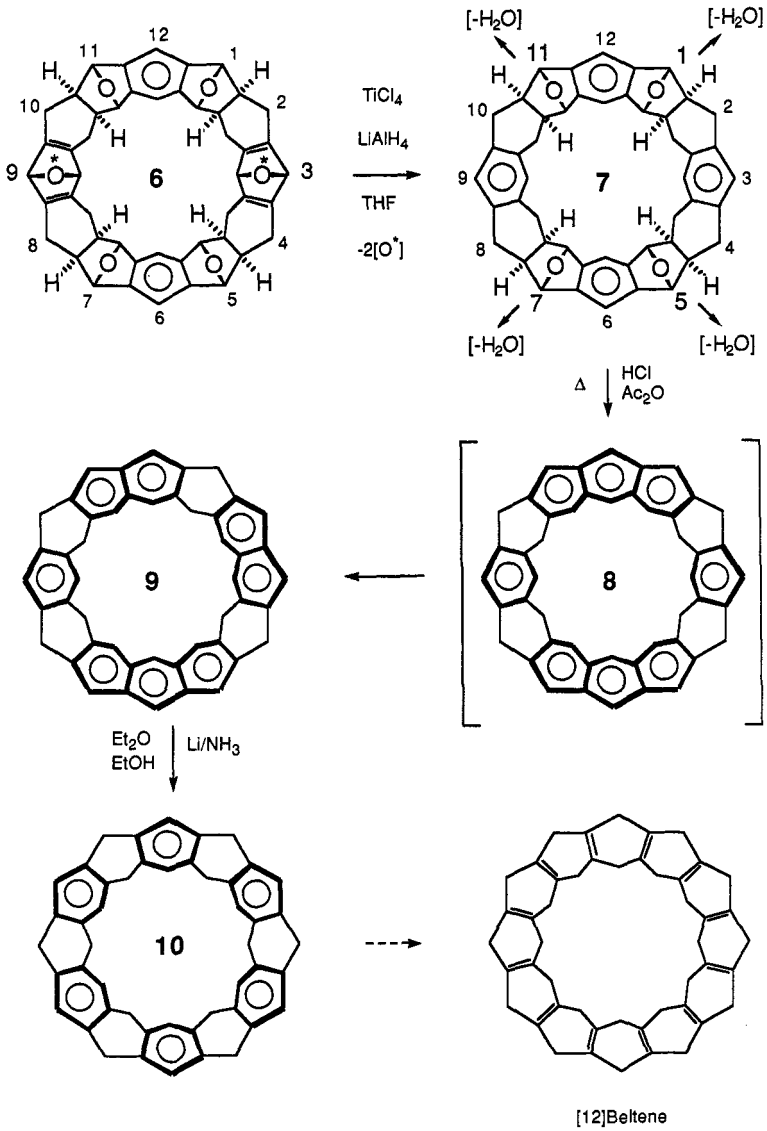
WORKING ROUND THE CLOCK

The reaction steps outlined in Scheme 5 summarise how the macropolycycle **6** can be converted into the hydrocarbon **10** with 6 benzene rings in an alternating cyclic array. We have christened[4] this compound [12]collarene. A clock numbering system, as employed in Scheme 5, is useful in referring to the reaction pathway, **6** → **7** → **8** → **9** → **10**. Whilst deoxygenation at 3 and 9 o'clock proceed smoothly to afford **7**, dehydration of **7** is accompanied by some reshuffling of the aromatic rings so that, instead of isolating **8**, with 2 anthracenes and 2 benzenes, the hydrocarbon **9** with 2 naphthalenes, 1 anthracene, and 1 benzene is obtained. Reduction of **8** under mild Birch conditions affords [12]collarene (**10**), which is, of course, a precursor of [12]beltene.

MOLECULAR RECEPTORS

The X-ray crystal structures of both **6** and **7** have been determined[3,4] (Fig. 1). In the case of **7**, a 'free' water molecule is trapped inside its Celtic cross-like hydrophobic cavity with its hydrogen atoms > 2.7 Å away from any potentially interactive sites. Although **6** does not form an inclusion compound with its solvent (chloroform) of crystallisation, it has been successfully employed[10] as a detector coating for the selective piezoelectric quartz crystal detection of nitrobenzene.

Scheme 5



The conversion of the macropolycycle **6** into [12]collarene (**10**). Note that a clock numbering system can be used to identify the six-membered rings in [12]cyclacene derivatives.

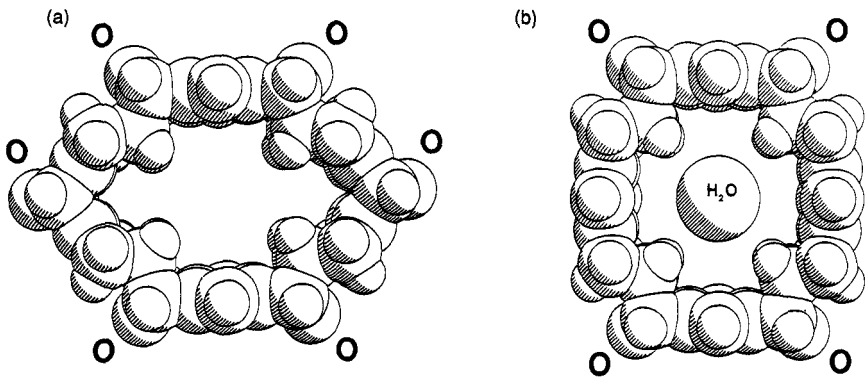


Fig. 1. Space-filling representation of the solid state structures of (a) the macropolycycle **6** and (b) its dideoxy derivative **7** with an included disordered water molecule which is represented as a sphere with radius equivalent to the envelope of a water molecule.

FUTURE PERSPECTIVES

The discovery that compounds such as the macropolycycle **6** can be produced efficiently in gram quantities opens up a great deal of exciting new possibilities[9,11] in synthetic, structural, and receptor chemistry. As we have already stated[9] elsewhere . . . .

" . . . the opportunity exists to ring the structural changes on compound **6** *ad infinitum*. Molecular belts, big and small, molecular cages, little and large, and molecular strips, linear and coiled, not to mention molecular nets and stacks, all start to swarm into the mind of the chemist attracted by the uncharted territory of unnatural product synthesis.[12] The fact that the synthetic chemist can create molecular materials that are rigid, ordered, and large, without having to resort to complicated multistep syntheses using expensive reagents and often employing difficult to remove templates as structural scaffoldings is an intriguing and exciting prospect. The generality and usefulness of this concept will depend on just how many different sets of molecules can be programmed to express themselves through their mutual reactions in unique structural fashions without extensive reagent control."

Acknowledgements

We are deeply indebted to Dr Neil S. Isaacs (University of Reading) for his assistance in performing high pressure reactions, to Mr Peter R. Ashton (University of Sheffield) for helping to identify many new compounds in the first instance by fast atom bombardment mass spectrometry, and to Dr David J. Williams and Miss Alexandra M.Z. Slawin (Imperial College London) for their rapid solutions to many awkward X-ray crystal structures. Much of the experimental data, on which this article is based, was obtained because of their enthusiastic cooperation. We thank the Science and Engineering Research Council, the Ministry of Defence, and the Johnson Matthey Technology Centre in the United Kingdom, and the University of Messina in Italy for their generous financial support. One (J.F.S.) of us acknowledges the award of a Research Fellowship from the Leverhulme Trust.

REFERENCES

1. D.J. Cram, *Science 219*, 1177-1183 (1983); *Angew. Chem. Int. Ed. Engl. 25,* 1039-1057 (1986); *Science 240*, 760-767 (1988); *Angew. Chem. Int. Ed. Engl. 27*, 1009-1020 (1988).
2. O. Diels and K. Alder, *Ann. Chem. 460,* 98-122 (1928).
3. F.H. Kohnke and J.F. Stoddart, *Abstracts of 194th American Chemical Society National Meeting,* New Orleans, 30 Aug - 4 Sept 1987, CARB 32; F.H. Kohnke, A.M.Z. Slawin, J.F. Stoddart and D.J. Williams, *Angew. Chem. Int. Ed. Engl. 26*, 892-894 (1987).
4. P.R. Ashton, N.S. Isaacs, F.H. Kohnke, A.M.Z. Slawin, C.M. Spencer, J.F. Stoddart and D.J. Williams, *Angew. Chem. Int. Ed. Engl. 27,* 966-969 (1988).
5. R.W. Alder and R.B. Sessions, *J. Chem. Soc., Perkin Trans. 2*, 1849-1854 (1985).
6. H. Hart, N. Raja, M.A. Meador and D.L. Ward, *J. Org. Chem. 48*, 4357-4360 (1983); F.H. Kohnke, J.F. Stoddart, A.M.Z. Slawin and D.J. Williams, *Acta Cryst. C44*, 738-740 and 742-745 (1988).
7. P. Vogel and A. Florey, *Helv. Chim. Acta 57,* 200-204 (1974); P.-A. Carrupt, J.-P. Hagenbuch, A. Florey and P. Vogel, *Helv. Chim. Acta 63*, 1149-1157 (1980).
8. W.H. Watson (Ed), *Stereochemistry and Reactivity of Systems containing π-Electrons,* Verlag Chemie, Deerfield Beach, Florida (1983): in particular, the articles by K.N. Houk (p.1), L.A. Paquette (p.41), R. Gleiter and M.C. Böhm (p.105) and P. Vogel (p. 147).
9. P. Ellwood, J.P. Mathias, J.F. Stoddart and F.H. Kohnke, *Bull. Soc. Chim. Belg.,* In press.
10. M.A.F. Elmosalamy, F.H. Kohnke, G.J. Moody, J.F. Stoddart and J.D.R. Thomas, *Analytical Proceedings,* Submitted.
11. J.F. Stoddart, *J. Incl. Phenom.*, In press; *Chem. Brit.*, In press.
12. J.F. Stoddart, *Nature 334*, 10-11 (1988).