New Adventures in the Synthesis of Hetero-Bridged *syn*-Facially Fused Norbornadienes ("[*n*]Polynorbornadienes") and Their Topological Diversity

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Molecular Scaffolds formed by the linking of bicyclo[2.2.1]-heptane (norbornane) subunits by sharing a common C_2-bridge have great appeal to the molecular architect since modelling studies have shown that the *syn*-facially fused members have a curved topology. Furthermore, this curvature can be modified by replacement of the methylene bridge by heteroatom bridges (O, S, NR), and made rod-like by introducing a σ-bond between adjoining methylene bridges in sesquinorbornane subunits. This review presents synthetic methodology which allows the stereocontrolled construction of [*n*]polynorbornanes and their hetero-analogues. Whereas Diels–Alder cycloadditions involving *N*-substituted pyrroles and isoindoles have been used to access the [2] and [3]polynorbornanes, the longer framed [3]–[10]polynorbornanes have been prepared using newly developed 1,3-dipolar cycloaddition strategies. These reactions depend on the formation of 1,3-dipolar intermediates by the thermal ring-opening of substituent-activated cyclobutene epoxides and aziridines and their trapping with norbornenes and related ring-strained dipolarophiles.

1. Introduction

The advent of supramolecular chemistry has heightened our awareness of the role played by component geometry in the effective building of molecular arrays. Indeed, it is the topology of the components, together with the geometrical requirements of the noncovalent bonding process (planarity for H bonding; specific geometries for metal complexation, coplanarity for π-stacking etc.), which dictates the effectiveness of molecular assembly, as well as the final 3D-structure.[1]

Our group has an ongoing interest in both molecular assembly[2] and the synthesis of the substrates used in the assembly process, especially those with novel topologies.[3] The present Microreview concentrates on the synthesis, design and topology of molecular frames based on norbornanes and their 7-hetero-bridged analogues, fused together by sharing a common C_2 bridge of the bicyclo[2.2.1]heptane. Accordingly, at each junction point the two adjacent norbornanes can have four different geometries, two with the methylene bridges *syn*-facial and two with the methylene bridges *anti*-facial, thereby offering a range of individual frames; the sesquinorbornadiene isomers **1**–**4** illustrate this feature (Figure 1).

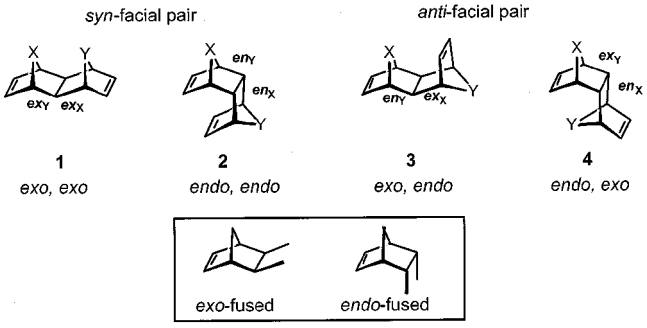

Figure 1. Nomenclature for sesquinorbornanes isomers

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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We[4,5] and others[7–11] have exploited the Diels–Alder addition of cyclic 1,3-dienes to norbornadienes to access sesquinorbornadienes, where the lack of stereoselectivity has allowed the formation of a variety of geometrical products. This approach is excellent for the preparation of these [2]polynorbornanes, but is not suitable for larger systems. In the latter area, development of our (A+B) "lego" block building approach to synthesis has been particularly rewarding.[12] In this methodology, norbornenes or 7-hetero-bridged norbornenes, e.g. **5**, serve as the 2π-reagents (the A-blocks) which are coupled with complementary norbornene-fused 4π-reagents, e.g. **6** (the B-blocks), in [4π + 2π] cycloaddition reactions (the 1,3-dipolar version is illustrated in Figure 2a). The *exo,exo*-stereoselectivity in most of these reactions has allowed access to *syn*-facial 7-hetero-polynorbornane systems for use as polarofacial systems (vide infra). The potential of this assembly protocol was expanded by the development of hetero-bridge-containing B-blocks (**6**; Z = O, NR) as well as by the preparation of dual blocks, e.g. **8** or **9**, which have 1,3-dipolar or alkene coupling functionalities, respectively, at both ends of the molecule. The dual block technique has provided alternative pathways to [*n*]polynorbornenes, illustrated here by entry to [5]polynorbornanes **9**, **10b** (Figure 2b).

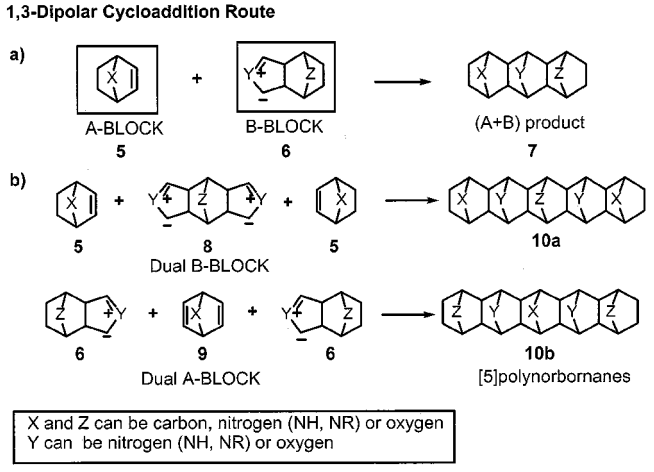


Figure 2. Schematic representation of the (A+B) block-coupling route to polynorbornanes

2. The [*n*]Polynorbornane Nomenclature

While the naming of fused norbornanes can be addressed using the von Baeyer nomenclature, it is convenient to have a common name for their everyday use. This is already the practice for the ring system derived from the fusion of two norbornane rings at the 2,3-positions, *viz* sesquinorbornane; however, this does not conveniently translate to compounds with higher numbers of fused norbornanes. We have coined the term "polynorbornane" as the generic name for these systems and propose a nomenclature related to that used for [*n*]ladderanes (see **16** and ref.[46]), combined with the classical heteroatom substitution "a" nomenclature (aza, oxa, thia, etc.) applied to alicyclic structures. Thus, the series of polynorbornanes **11–15** (Figure 3) are designated as [*n*]polynorbornanes in which the parenthesised number "*n*" reflects the number of component norbornane subunits. The hetero-bridged members of the [*n*]polynorbornanes, such as **18–20**, carry a prefix indicating the sequence of atoms in the bridges ordered from left to right (carbon bridges indicated by C). Thus, compound **18** becomes CNO-[3]polynorbornane, while the all-oxygen-bridged system **20** becomes O^5-[5]polynorbornane. This nomenclature relates only to the *exo,exo*-fused polynorbornanes; where the geometry differs from this standard, we propose the use of the term "*iso*" as a prefix, e.g. compound **17** becomes [4]isopolynorbornane.

3. *syn*-Facial Sesquinorbornadienes Including Those With Hetero-Bridges

The synthesis of the parent *syn*-facial sesquinorbornadiene **1** was first reported in 1986.[13] This route starts from norbornenone **21** and was elaborated to the final product in six steps, a process that involves skeletal rearrangement

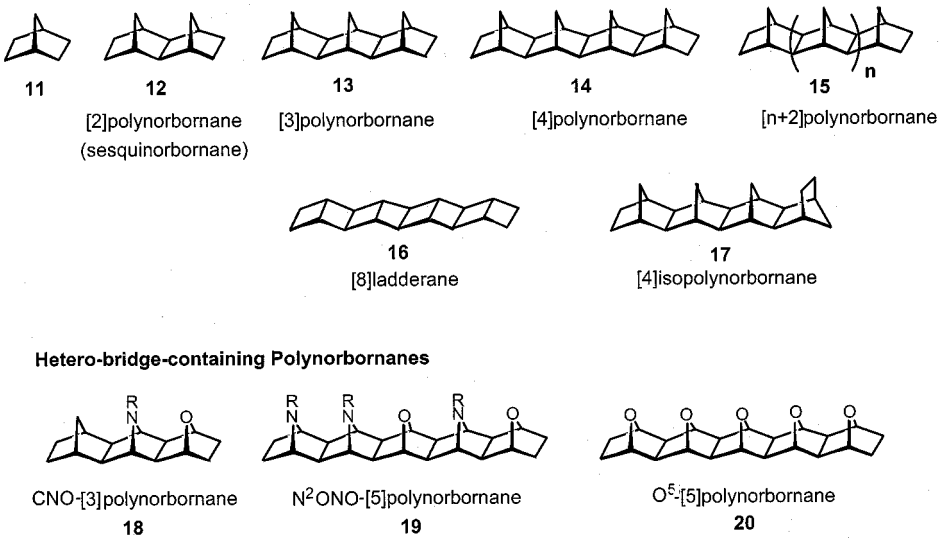
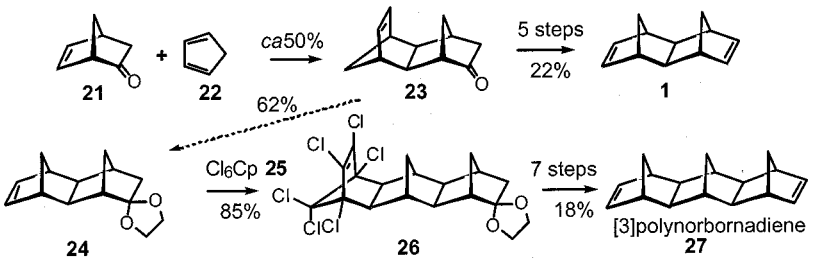


Figure 3. Representative [*n*]polynorbornanes



Scheme 1

of the intermediate *anti*-sesquinorbornanone **23** (Scheme 1). The propensity of cyclopentadiene to form *exo, endo*-adducts with norbornenes frustrated its use for direct entry to **1** by addition of cyclopentadiene to norbornadiene.[14]

The hexacyclic system with three fused norbornanes, C^3-[3]polynorbornadiene **27**, was also reported and again a rearrangement strategy was required to effect the synthesis and involved seven steps from the ketal **26**.[13] As this route is multi-step and the overall yield is low (9% from **23**), this makes C^3-[3]polynorbornadiene **27** (or sesquinorbornadiene **1**) a poor choice as a starting material in further synthesis.

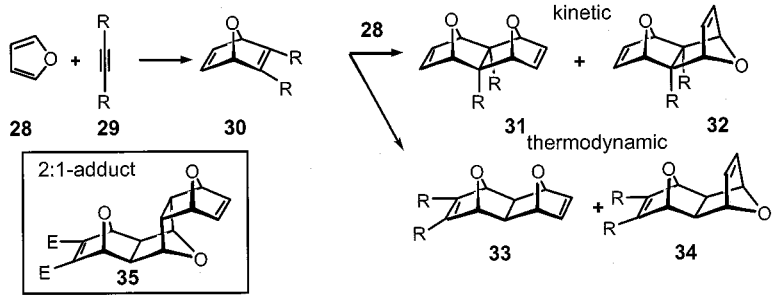
In the heterobridged sesquinorbornane series, most early work was conducted around the cycloaddition of furan with 7-oxanorbornadiene derivatives. The pioneering work by LeGoff[6] and later by McCulloch,[7] involved the reaction of furan **28** with dimethyl 7-oxanorbornadiene-2,3-dicarboxylate **(30a)**. This reaction, which produces the 1:1-adducts **31**−**34**, 2:1 adducts such as **35**, and even higher adducts, forcefully established the accessibility of oxa-bridged sesquinorbornadienes (Scheme 2). The reluctance to form *syn*-facially-bridged products by this method, especially when methyl substituents are attached to the diene or the dienophile (at the bridgehead), became part of the folklore. This tenet was challenged by our related study on the reaction of furan with 2,3-bis(trifluoromethyl)-7-oxanorbornadiene **(30b)** which produces a kinetically controlled mixture rich in the *syn*-facial adduct **31b** at room temperature (**31b:32b** = 4:3), and the thermodynamically controlled adducts favouring the *anti*-facial isomer **34b** at 120 °C (**34b:33b** = 2:1) (Scheme 2).[15]

Indeed, there was evidence in the earlier literature that cycloaddition of furan could afford exclusively *syn*-sequinorbornadienes. Specifically, Diels and Alder reported in the 1930's that the reaction of furan with acetylene dicarboxylic acid **(29c)** gives a 2:1-adduct in high yield.[8] This product was subsequently shown to have the *syn*-facial structure **31c**,[8,9] thereby demonstrating that oxygen-bridges could be juxtaposed, given the right circumstances.

The difference between the two types of experiment stems from the fact that production of the Diels−Alder product **31c** is solubility driven, being formed by mixing the reagents together in ether at room temperature: the product crystallised from the reaction mixture over several weeks. It has been shown recently that 2-methylfuran **36** also undergoes a similar cycloaddition with acetylene dicarboxylic acid **29c** to form adduct **38** where both the stereochemistry and regiochemistry are solubility-controlled (Scheme 3).[10]

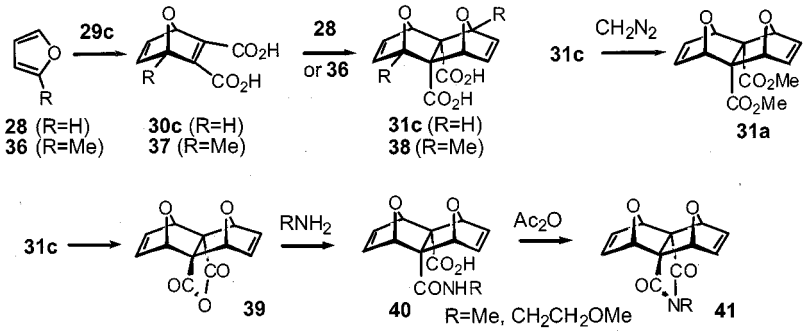
The sesquinorbornadiene diacid **31c** can be accessed in quantity using the above method and serves as an excellent starting material for producing the related *syn*-facial diester **31a** and the *syn*-facial anhydride **39**.[16] The latter compound is used to access the related imides **41**[17] by way of the respective amic acids **40** (details, Scheme 3). We have used anhydride **39** and imides **41** as bis-alkene reagents in applications requiring moderately high temperatures since these cyclic systems are less prone to reverse Diels−Alder fragmentation than the diester **31a**, which lacks the stabilising effect of the additional five-membered ring.

We appreciated that all of the above-mentioned cycloadditions which give soluble products are complicated by adduct reversibility and, since product mixtures change at different temperatures, reflect combinations of kinetic and thermodynamic control of isomer compositions. Accordingly, we sought new routes to sesquinorbornadienes using highly reactive starting materials, so that milder conditions could be employed and kinetic factors would control stereochemical outcomes. This has the advantage that product ratios would be constant and, furthermore, may be predictable using computational methodology.



Series a R=CO_2Me; Series b R=CF_3; Series c R=CO_2H; Series d R=CO_2*tert*Bu

Scheme 2

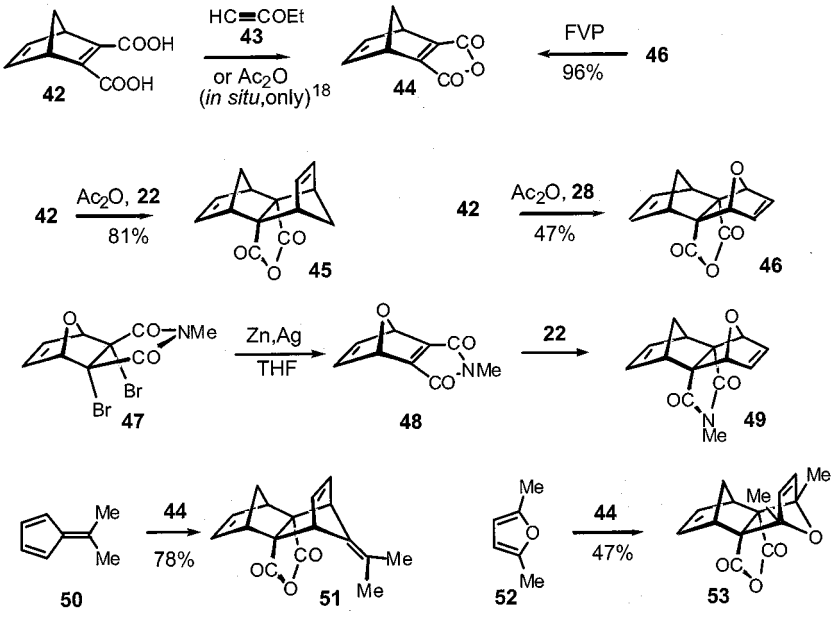


Scheme 3

Support for this premise came from Edman and Simmons who reported[11c] that anhydride **44** [formed from the diacid **42** with ethoxyacetylene **(43)**] reacts site-selectively at the anhydride π bond with cyclopentadiene **(22)** to give two *exo*-adducts, and that the *anti*-bridged *exo,endo*-adduct **45** is the dominant isomer (99:1). Bartlett et al.[11a,11b] subsequently reported that furan adds to norbornadiene-2,3-anhydride **(44)** to form the *syn*-bridged oxasesquinorbornadiene **(46)** in high yield. These studies confirmed the high reactivity of norbornadiene anhydrides at the anhydride π centre. Furthermore, since both reactions occur at room temperature, the kinetically derived *syn*-facial products are stable and can be isolated in high yields. In recent work we have found that adduct **46** can be prepared by warming diacid **42** (Scheme 4) with acetic anhydride containing furan according to the method of Williams.[18] Flash vacuum pyrolysis (FVP) of adduct **46** allows rapid access to the anhydride **44**, and serves as an alternative route to obtain anhydride **44** in crystalline form. Anhydride **44** was shown to react smoothly with 6,6-dimethylfulvene **(50)**, to form predominantly the *anti*-adduct **51**, and with 2,5-dimethylfuran **(52)**, to produce the related *anti*-adduct **53**.[19] Thus, the introduction of methyl groups at the 2,5-positions of furan can be used to reverse the stereoselectivity.

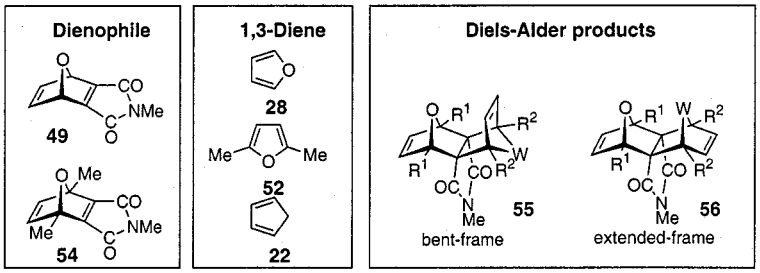
Because of the difficulty of producing norbornadiene anhydride at the time, we initiated a study of the reaction of cyclic 1,3-dienes with the related 7-oxanorbornadienomaleimides **48** and **54**, since they can be accessed by an alternative route. This method involves debromination (Zn, Ag couple) of adduct **47**, formed by reaction of furan with *N*-methyl-3,4-dibromomaleimide.[4] *N*-methyl-7-oxanorbornadienomaleimide **(48)**, generated in this way, is too unstable for isolation, but can be trapped in situ and forms adducts with cyclopentadiene **(22)**, furan **28** and 2,5-dimethylfuran **(52)** (for product ratios, see Table 1). The dimethyl derivative **54** is more stable and can be isolated in crystalline form.[20]

The incorporation of the oxygen bridge into the norbornadienomaleimide substantially changes the 1,3-diene cycloaddition stereoselectivities and reaction rates. Preferential formation of *anti*-bridged cycloadduct **55a** is now observed in the reaction of furan with **49**, whereas almost exclusive formation of the *syn*-bridged product **56c** occurs in the addition with cyclopentadiene. These results demonstrate that the stereoselectivity of the furan cycloaddition is unlikely to be sterically controlled, but rather reflects an adverse O,O-orbital interaction operating in the transition state, thereby leading to the *anti*-isomer becoming the pre-



Scheme 4

Table 1. Stereoselectivities in the cycloadditions of 7-oxanorbornadienomaleimides **49** and **54** with cyclic 1,3-dienes; theoretical predictions are in bold in the E_a column; the experimentally preferred adduct is in bold



Reactants	product ratio (55:56)	E_a §	series	R^1	R^2	W	R^1	R^2	W
				55a-e			56a-e		
49 + 28	60:40	**105.8**; 106.5	a)	**H**	**H**	**O**	H	H	O
49 + 52	30:**70**	124.6; **120.7**	b)	H	Me	O	**H**	**Me**	**O**
49 + 22	5:**95**	123.0; **117.1**	c)	H	H	CH_2	**H**	**H**	**CH_2**
54 + 28	**80**:20	**111.4**; 112.5	d)	**Me**	**H**	**O**	Me	H	O
54 + 52	**>99**:1	**130.9**; 150.0	e)	**Me**	**Me**	**O**	Me	Me	O

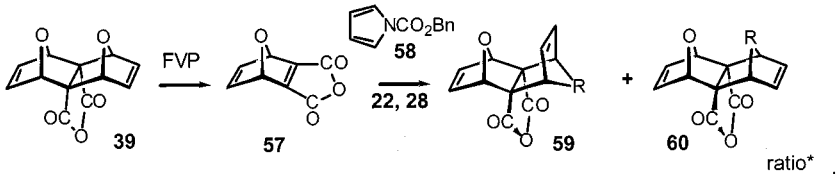
§ AM1 Activation energies in $kJmol^{-1}$

ferred kinetic product. This orbital/orbital effect is not dominant over other steric effects, as a significant change in stereoselectivity occurs when substituents are positioned on the diene or the dienophile (or both). In this way, significant control of adduct geometry can be achieved (see Table 1). For example, the *syn*-facial bis(oxygen-bridged) product **56b** can be obtained by direct addition of 2,5-dimethylfuran **(52)** to **49**, whereas similar addition of **52** to the dimethyl-substituted dienophile **54** gives exclusively the *anti*-facial product **55c**. In this series, the stereoselectivities could be predicted using AM1 calculations of the energy for the competing transition states.[4] The semiempirical method has been applied successfully in related cycloadditions involving pyrroles (see Scheme 8); in this case, the PM3 method was preferred.[5]

While we have used the acetic anhydride cyclisation technique[18] to access new norbornadiene anhydrides in situ, this method for producing **57** is not useful owing to the difficulty in accessing the diacid **30c**. Instead, we have used flash vacuum pyrolysis of the readily available furan adduct **39** as the preferred route to **57** (Scheme 5). A feature of 7-oxanorbornadiene anhydride **(57)** is its high dienophilic reactivity, which allows access to the *exo,syn*-adducts **59** and *exo,anti*-adducts **60** by reaction with cyclopentadiene **(22)**, furan **28** or *N*−Cbz-pyrrole **58** at room temperature. The product ratios presented in Scheme 5 have been determined by ^{1}H NMR spectroscopy on reaction mixtures; however, the individual isomers have not been separated. Furthermore, **57** also reacts with anthracene at a little above room temperature, whereas the carbocyclic counterpart **44** is reported to require overnight heating under reflux in xylene solution to effect cycloaddition.[11c]

A similar dichotomy between the reactivity of norbornadiene anhydride **44** and 7-oxanorbornadiene anhydride **(57)** is evident in their reaction with pyrroles, where norbornadiene **44** fails to react with *N*−Cbz-pyrrole even at high temperatures, whereas addition to **57** occurs at room temperature. Interestingly, *N*−Cbz-7-azanorbornadiene anhydride **(78)** (for synthesis, see Scheme 10) also reacts with *N*−Cbz-pyrrole **(66f)** to form *syn*-facial products (vide infra). These observations proffer a π bond-activating role for the oxygen bridge in **57** and the nitrogen bridge in **78**, yet this factor remains to be determined.

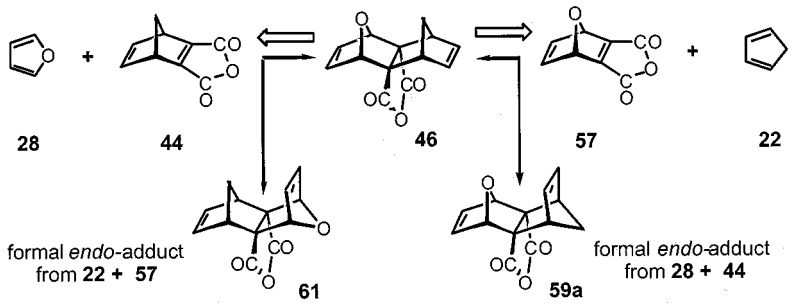
The availability of **57** set the scene to illustrate the concept of "parity inversion" in sesquinorbornadiene synthesis.[21] Using adduct **46** as a prototype sesquinorbornadiene with different bridges, it is possible to identify two equivalent retrosynthetic schemes leading to a norbornadiene anhydride and a



			ratio*
Series a) R=CH_2	**59a**	**46**	1:2
Series b) R=O	**59b**	**39**	3:1
Series c) R=NCO_2Bn	**59c**	**60c**	1:99

* determined by ^{1}H NMR

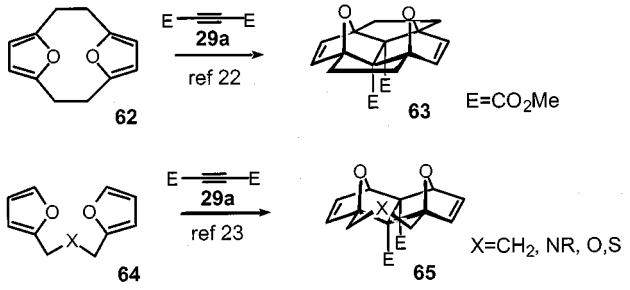
Scheme 5



Scheme 6

complementary cyclic 1,3-diene (Scheme 6). These pairs (**28** + **44** and **22** + **57**) are related by interchange of the 7-substituent of the norbornadiene with the 5-substituent of the cyclic diene. Hence the two retrosynthetic pairs have parity in regard to reagent type and are transformed one to the other by a simple atom (or substituent) interchange. The subtlety in this concept lies, not in the fact that both parity pairs yield the same *syn*-facial adduct, but that the accompanying *exo,endo*-adduct of one pair is the formal *endo*-adduct of the parity inverted pair, e.g. **61** in relation to **22** + **57**, and **59a** in relation to **28** + **44**. This opens synthetic opportunities to access *anti*-sesquinorbornadienes of type **3** and **4** (Scheme 1), which are not available directly since *endo*-attack on norbornenes is rarely observed as a major pathway.

Methods have been developed which ensure that *syn*-facial cycloaddition can be used in the production of some modified sesquinorbornadienes. In the first of these, Cram 24 reported [22] that the furanocyclophane **62** reacts with dimethyl acetylenedicarboxylate **(29a)** to form the *syn*-facial adduct **63** exclusively (Scheme 7).

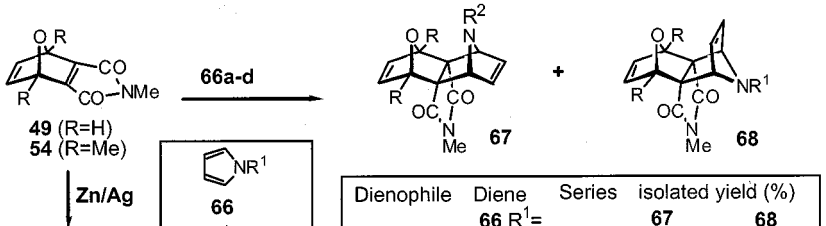


Scheme 7

Subsequently, Lautens has shown[23] that a single 1,3-propylene linkage (**64**, X = CH_2) is sufficient to ensure *syn*-facial control and formation of **65** (X = CH_2). The length of the linking chain is critical to the success of the conversion of **64** to pincer adduct **65** (C_3 works; C_2 and C_4 fail), however, the three atom link (CXC) can tolerate heteroatoms (X = NR, O, S).

As part of our block-building synthesis program employing 1,3-dipolar[3,24] coupling procedures (Section 5), we have sought other hetero-bridged sesquinorbornadienes as dual alkene reagents for reaction with epoxide or aziridine partners (Scheme 24). In this regard, we have changed emphasis from the oxygen-bridged series to those containing one or two nitrogen bridges and, as a consequence, the role played by pyrroles in cycloaddition chemistry became paramount.[25]

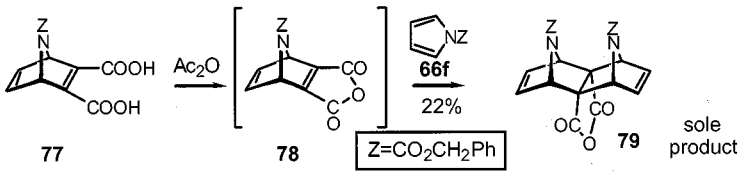
Initial experiments were conducted in the mixed N,O-bridged series using the 7-oxanorbornadienomaleimide **49**, where it was found that *N*-acetylpyrrole **(66b)** produces exclusively the *syn*-facial product **67b**, albeit in poor yield (Scheme 8). In an interesting reversal of stereoselectivity, the *N*-trimethylsilylpyrrole **(66c)** affords exclusively the *exo,endo*-product **68c**, a fact attributed to the steric effect of the TMS substituent. In practice, the deprotected product **68a** is isolated from the reaction, rather than **68c**, owing to the lability of the TMS group under the work-up conditions. The poor yield in these cycloadditions is partly attrib-



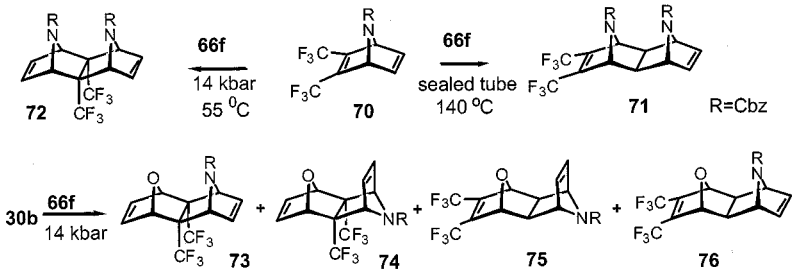
Dienophile	Diene 66 R^1=	Series	isolated yield (%) 67	68
49 (R=H)	H	a	-	-
	COMe	b	15	-
	$SiMe_3$	c	-	10†
54 ($R=CH_3$)	H	a	40	trace
	COMe	b	29	12
	$SiMe_3$	c	29†	11†
	Me	d	21	16

† isolated as NH compound

Scheme 8. Addition of *N*-substituted pyrroles to 7-oxanorbornadieneomaleimides **49**, **54**



Scheme 10



RT	5 days	14 kbar	100%§	0	0	0
55 °C	4 days	14 kbar	94%§	0	0	4%§
90 °C	2 days	14 kbar	56%§	0	7%§	27%§
130 °C	3 days	1 atm	0	0	3%¶	62%¶

§ Yields are determined by spectroscopy ¶ isolated yields

Scheme 9. Formation of hetero-substituted sesquinorbornadienes using Diels–Alder cycloadditions at high pressure

uted to the competitive deoxygenation reaction which converts the 7-oxanorbornadienomaleimides **49** and **54** into their respective phthalimides **69**.

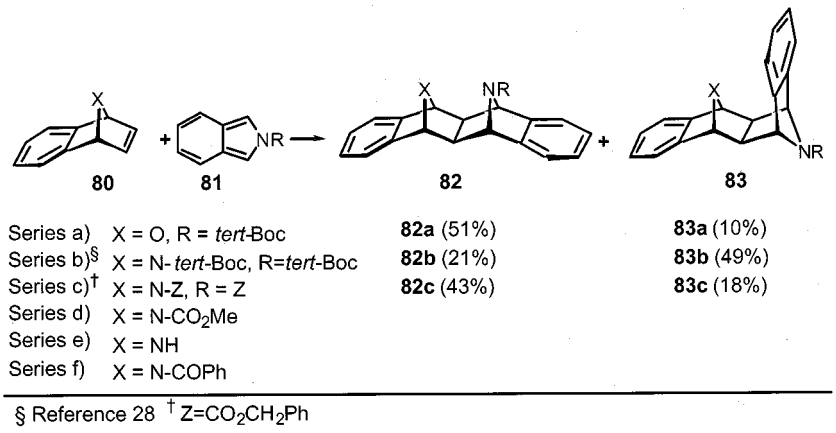
The more stable methyl-substituted dienophile **54** gives better yields with the *N*-substituted pyrroles **66a–d** and, even more interestingly, favours formation of the *syn*-facial isomers (Scheme 8). The stereoselectivities of these reactions are quite at odds with the corresponding furan cycloaddition (vide supra, Table 1) and further reinforce the emerging rule that N,O-interactions in transition states leading to *syn*-bridged cycloaddition products are not hugely repulsive.

High-pressure chemistry has played an important role in the production of [4 + 2] cycloadducts from *N*-substituted pyrroles,[25b] and this is certainly our experience in the quest for diazasesquinorbornadienes. The *N*–Cbz-pyrrole **(66f)** is reluctant to react with the *N*–Cbz-7-azanorbornadiene **70** and requires heating in a sealed tube at 140 °C to effect a reaction. The *syn*-facial product **71** (Scheme 9) is formed by reaction at the unsubstituted π bond of **70.** In contrast, reaction occurs at considerably lower temperature (55 °C) under high pressure (14 kbar), except that these same reagents form the isomeric *syn*-facial adduct **72** by attack at the trifluoromethyl-substituted π bond. The use of ultra high pressures (10–15 kbar) is also required for addition of the *N*–Cbz-pyrrole **(66f)** to the corresponding 7-oxanorbornadiene **30b**. Reaction at room temperature under high pressure gives exclusively the *syn*-facial adduct **73** by reaction at the trifluoromethyl-substituted π bond. When the temperature is raised to 55 °C, a new *syn*-facial adduct **76** is produced by reaction at the unsubstituted π bond, together with **73**. Raising the temperature to 90 °C sees the emergence of a third adduct **75** and gives the first evidence for *anti*-sesquinorbornadiene production in this series. All these results can be interpreted in terms of kinetic attack at the trifluoromethyl-substituted π bond to form adducts which undergo isomerisation to yield thermodynamically driven products at the unsubstituted π bond.

The most effective route to *syn*-facial diazasesquinorbornadienes is through addition to the 7-azanorbornadiene-2,3-dicarboxylic anhydride **78** (Scheme 10). Thus, treatment of diacid **77** with acetic anhydride at 65 °C in the presence of *N*–Cbz-pyrrole **(66f)** produces a single *exo*-adduct at the anhydride π bond, which is assigned the *syn*-facial structure **79** on the basis of the symmetry of the ^{1}H NMR spectra at elevated temperature.

4. Hetero-Bridged Benzosesquinorbornadienes

The work of Sasaki,[26] modelled after the earlier study reported by Fieser and Haddadin in the O,O-series,[27] was the flagship in the area of *N*-hetero-bridged benzo-fused sesquinorbornanes. Entry to N,O-bridged and ,N-bridged [2]polynorbornanes was achieved by reaction of *N*-Boc-isoindole **81a** with the π bond of 7-oxa-benzonorbornadiene **(80a)** or *N*-Boc-7-azabenzonorbornadiene **(80b)** (Scheme 11). While mixtures were reported in each case, the *syn*-facial isomer **82a** is preferred in the N,O-series, whereas the *anti*-facial product **83b** is dominant in the N,N-series. The preference for the turn-frame isomer **83b** is exceptional



Scheme 11. *N*-substituted isoindole cycloadditions

in N,N-bridged systems and may reflect the steric bulk of the Boc substituents. Since two Cbz groups are apparently less sterically demanding and yield *syn*-facial products in related pyrrole cycloadditions (see Scheme 7), we reacted *N*−Cbz-7-azabenzonorbornadiene **(80c)** with *N*−Cbz-isoindole **(81c)**. Significantly, two adducts are formed and the *syn*-facial adduct **82c** is dominant.

Malpass et al. have reported that cyclopentadiene and 1,3-cyclohexadiene react exclusively at the *exo*-face of *N*-substituted 7-azabenzonorbornadienes to produce *exo,endo*-adducts exclusively.[28] Subsequent theoretical studies by our groups have shown that these reactions are under kinetic control and that the stereoselectively can be predicted using either semiempirical or ab initio evaluations of relative activation energies.[29]

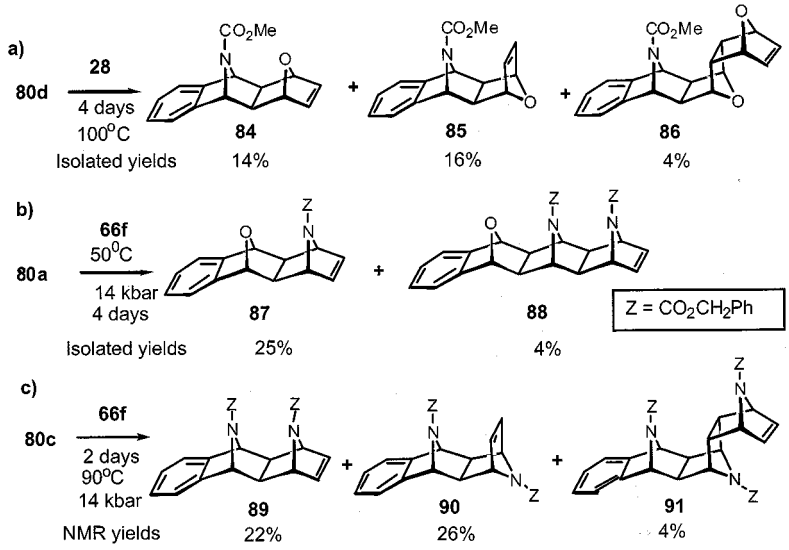
We have since investigated the reaction of furan with similar 7-aza-benzonorbornadienes (Scheme 12a). Reaction of furan with **80d** proceeds slowly under thermal conditions (sealed tube, 100 °C, 4 days) to afford the *syn*-facial 1:1-adduct **84** and the *anti*-facial isomer **85** in rougly equal amounts. A 2:1 adduct **86** is also produced, derived from further addition of furan to isomer **85**.

In an alternative approach to the N,O-series, *N*−Cbz-pyrrole **(66f)** was reacted with the 7-oxabenzonorbornadiene **80a** (Scheme 12b). This cycloaddition is more difficult and requires heat and high pressure to ensure reaction, whence exclusive formation of *syn*-facial adduct **87** and the related ONN-[3]polynorbornane **88** was observed.

The corresponding reaction of *N*−Cbz-pyrrole **(66f)** with the 7-azabenzonorbornadiene **80c** (Scheme 12c) also requires heat and pressure to achieve cycloaddition. While the reaction proceeds in better overall yield (52% overall), the *anti*-facial products **90** and **91** are again dominant (3:2) over the *syn*-facial adduct **89**.

5. The New Era: 1,3-Dipolar Cycloaddition Routes to Polynorbornanes

In the previous sections, we have concentrated on Diels−Alder cycloadditions to gain entry to sesquinorbornanes. A feature of that approach has been the almost universal lack of stereocontrol available to such cycloadditions, especially where the desired *syn*-facial products are kin-



Scheme 12

etically derived, yet forcing reaction conditions are required for the reaction to proceed. Accordingly, the *syn*-facial products are often only obtained as minor components in reaction mixtures. The use of high-pressure conditions has been beneficial in some cases and substituent effects can be employed, but the latter are useful only when bent-frame products are required. The benefit of these studies lies in the potential use of certain sesquinorbornadienes as alkene reagents in the block-building program. The most positive feature was the evidence it provided for the compatibility of hetero-bridges to exist in the *syn*-facial geometry (N,N >N,O > O,O) and that continues to be carried forward in this second phase of the [*n*]polynorbornane program.

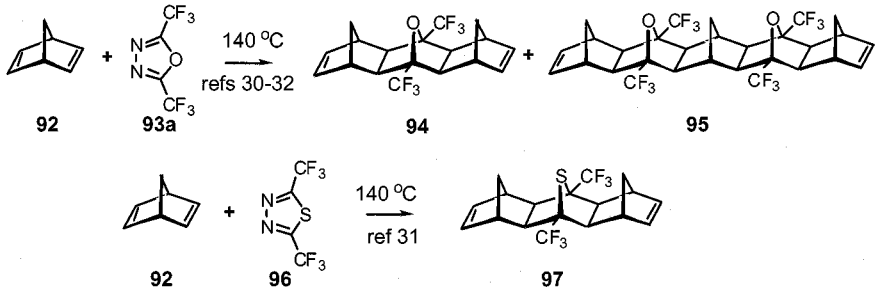
a) 1,3,4-Oxadiazole and 1,3,4-Thiazadiazole Cycloadditions

The first indications that [*n*]polynorbornanes containing oxygen bridges could be produced via coupling of bicyclic alkenes was provided by the use of 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole **93a**, which appeared contemporaneously from three different laboratories.[30−32] The ability of this chemistry to link two norbornadienes stereoselectively to produce the *syn*-facial COC-[3]polynorbornadiene **94** lay at the heart of this procedure and made an immediate impact on [*n*]polynorbornane synthesis (Scheme 13). Even more importantly, one of these research groups[30] also reported the co-formation of the COCOC-[5]polynorbornadiene **95** which served to herald the potential of 1,3,4-oxadiazole coupling and the compatibility of juxtaposed C,O-bridges to yield extended frame *exo,exo*-fused [*n*]polynorbornanes. It was also established that the coupling of norbornadiene could be achieved with the 1,3,4-thiadiazole **96**, which opened the way to produce polynorbornanes containing a sulfur bridge, e.g. CSC-[3]polynorbornane **97** (Scheme 13).[31]

Our own efforts to produce *syn*-facial poly-7-oxanorbornadienes **98a** from the coupling of 7-oxabenzonorbornadiene **80a** by treatment with the 1,3,4-oxadiazole **93a** were initially thwarted by exclusive formation of the *anti*-facial product **99a**. We attributed this outcome to the effect of adverse O,O-orbital/orbital interactions in the transition state for the second step of the coupling process which involves alkene addition to a 1,3-dipolar intermediate similar to **105**; E = CF_3, (Scheme 16).[33] We now know, however, that this explanation is simplistic since the *syn*-facial adducts **98b** and **98c** can be prepared from 1,3,4-oxadiazoles **93b** and **93c**, respectively, in which ester groups are substituted for one or both trifluoromethyl groups (see Tabulation in Scheme 14). This is another example where substituents have value in determining stereochemical outcomes.

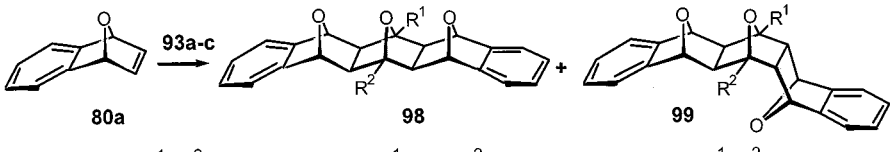
In subsequent studies, we have found that these cycloadditions can be conducted at ambient temperatures by working under high pressure (8−15 kbar),[33] thereby avoiding the high temperature (140−160 °C) required to effect cycloadditions thermally. This has been especially valuable in cycloadditions involving **80a**, which is isomerised to α-naphthol under the thermal conditions; we find that addition of triethylamine is also helpful in reducing this isomerisation.

1,3,4-Oxadiazole coupling of the related N-bridged system proved elusive as neither thermal nor high-pressure conditions worked. The breakthrough came when we found that a combination of each was successful. Thus, heating **80c** with 1,3,4-oxadiazole **93a** at 60 °C under a pressure of 14 kbar yielded the NON-[3]polynorbornane **100** and the



92 **93a** **94** **95** **92** **96** **97**

Scheme 13

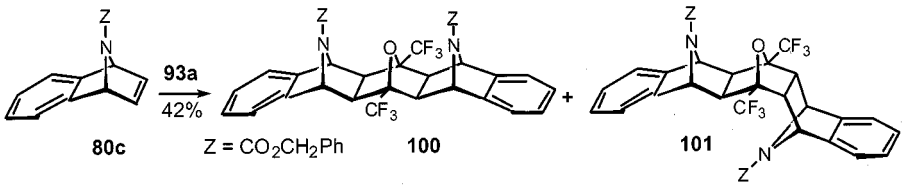


80a **98** **99**

Series a) R^1=R^2=CF_3 Series b) R^1=CF_3 R^2=CO_2Me Series c) R^1=R^2=CO_2Me

80a + 93a	0%	100%
80a + 93b	55%	45%
80a + 93c	60%	40%

Scheme 14



Scheme 15

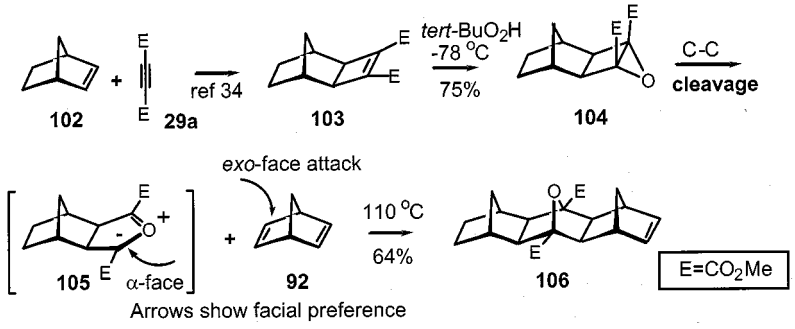
NON-[3]isopolynorbornadiene **101** in approximately equal amounts (Scheme 15).

b) The 1,3-Dipolar Cycloaddition Route to Fused 7-Oxanorbornanes (with R. A. Russell)

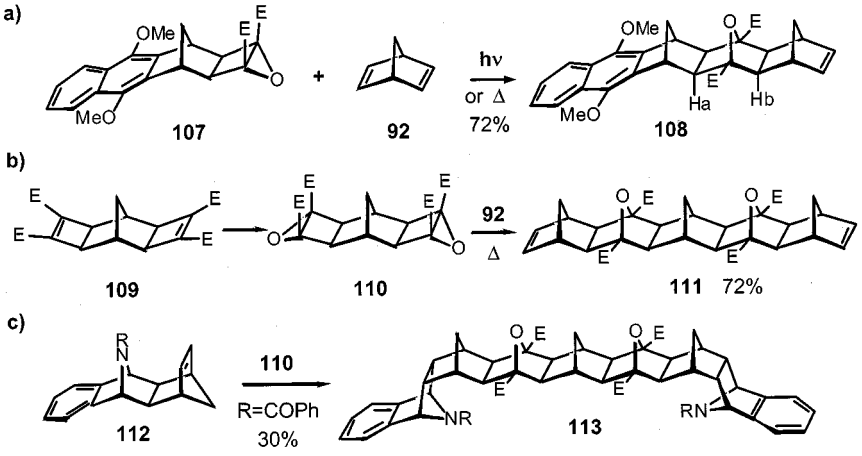
The advent of new 1,3-dipolar coupling reactions developed in our laboratory has made a significant impact on the synthesis of [*n*]polynorbornanes containing heterobridges.[24] The first reaction discovered[3] involved the cycloaddition of ring-strained alicyclic alkenes such as norbornenes and norbornadienes with ester-substituted cyclobutene epoxides such as **104** (prepared from norbornene **102** via adduct **103** is shown in Scheme 16). The mechanism of this reaction probably involves a 1,3-dipolar intermediate, e.g. **105**, which undergoes stereoselective [4π + 2π] cycloaddition with the alkene, e.g. norbornadiene **92**, under thermal conditions (140−160 °C) to produce a fused 7-oxanorbornane with ester groups at the bridgehead, e.g. **106**.

The synthetic potential of this reaction was expanded when it was found that certain of these 1,3-dipolar couplings could be effected at room temperature under photochemical conditions. Thus, irradiation (acetone, 300 nm) of a mixture of dimethoxynaphthaleno-fused epoxide **107** and norbornadiene **92** yielded the COC-[3]polynorbornadiene **108** (Scheme 17a). The same reaction could be effected under thermal conditions and, in each case, complete stereoselectivity was observed; a strong NOE between H_a and H_b served to establish the *exo,exo* stereochemistry.

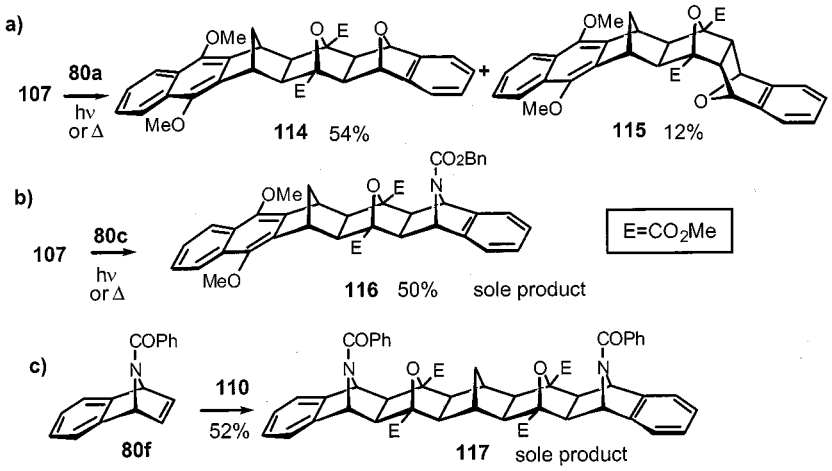
Dual extension methodology opened the way to a rapid and efficient entry to [5]polynorbornadienes (Scheme 17b). In this way, addition of norbornadiene **92** to the bis-epoxide



Scheme 16



Scheme 17



Scheme 18

110 (prepared by low temperature epoxidation of the known bis-cyclobutene 1,2-diester **109**[34]) affords the *syn*-facial COCOC-[5]polynorbornadiene **111** as the exclusive stereoisomeric product.

We have also exploited the *exo,endo* geometry of **112** [formed from the stereoselective addition of cyclopentadiene with *N*-benzoyl-7-aza-benzonorbornadiene **(80f)**] for the production of the cavity system **113** (Scheme 17c), a reaction which further confirms the usefulness of the dual 1,3-dipolar coupling protocol.

In view of the poor stereoselectivities observed in the Diel−Alder reaction of hetero-bridged benzonorbornadienes with heterocyclic 1,3-dienes, we were keen to check their stereoselectivities in 1,3-dipolar coupling protocols. In a set of prototype couplings, we reacted the epoxide **107** with 7-oxabenzonorbornadiene **(80a)** and found that the reaction is nonstereoselective and produces a mixture of the *syn*-facial COO[3]polynorbornane **114** and the stereoisomeric *anti*-facial product **115** (Scheme 18). The positive synthetic feature of this reaction is that the *syn*-facial adduct **114** is the major product.

More impressively, however, is the high stereoselectivity observed when aza-bridged norbornene derivatives are employed in this coupling reaction. Heating epoxide **107** with the *N*−Cbz-7-azabenzonorbornadiene **(80c)** gives the *syn*-facial CON-[3]polynorbornane **116** exclusively. This same *exo,exo* stereoselectivity is observed in the dual coupling of the *N*-benzoyl-7-azabenzonorbornadiene **(80f)** with bis-epoxide **110** thereby providing exclusive access to the NO-CON-[5]polynorbornane **117**.

c) The 1,3-Dipolar Cycloaddition Route to Fused 7-Azanorbornanes (with D. N. Butler and J. R. Malpass)

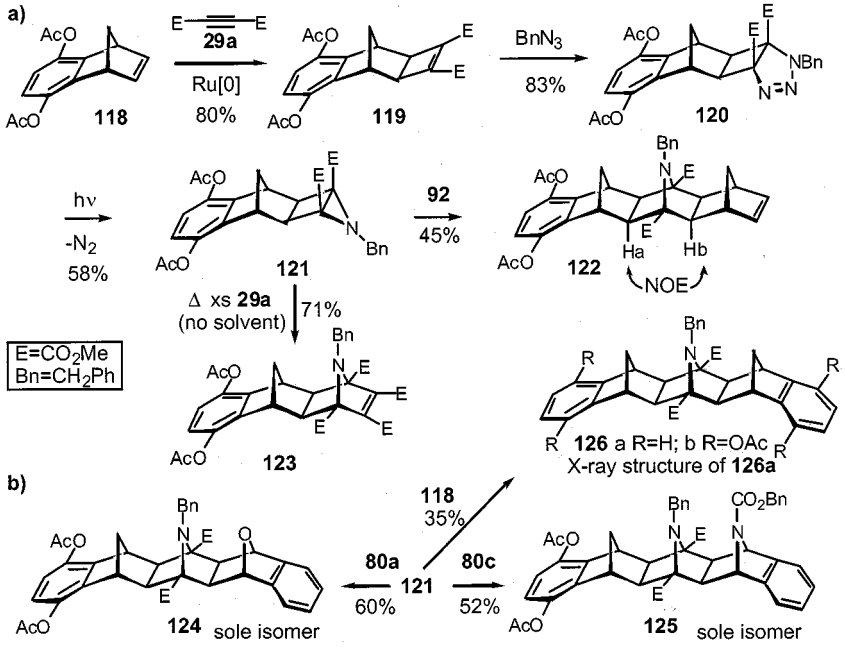
The replacement of the epoxide by an aziridine ring in the 4π-reagent provides a nitrogen analogue of the 1,3-dipolar cycloaddition reaction; again, the ester substituentson the three-membered ring are a requirement.[24] This new cycloaddition process allows coupling of the ring-opened aziridine with ring-strained alkenes to access 7-azanorbornanes, e.g. reaction of aziridine **121** with norbornadiene **(92)** (benzene at reflux) yields the stereoselectively coupled product **122** (Scheme 19a). The stereochemistry of **122** was confirmed by an NOE being observed between protons H_a and H_b. Production of the required aziridine **121** was achieved in two steps from the appropriate cyclobutene 1,2-diester, viz **119**. Thus, thermal addition of benzyl azide to **119** slowly yields the triazoline **120**, which was converted into the required aziridine **121** by photochemically-induced ejection of dinitrogen.

The aziridine **121** can also be used to access benzo[2]polynorbornadienes and this aspect is demonstrated by reaction of **121** with excess dimethyl acetylenedicarboxylate **29a** in the absence of solvent to afford the adduct **123** in good yield.

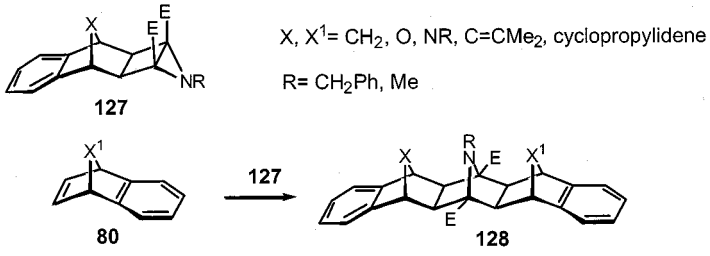
A similar reaction of aziridine **121** with hetero-bridged benzonorbornadienes **80a** and **80c** was extremely significant, since each reaction proceeds with complete stereoselectivity to yield the *syn*-facial hetero-bridged [3]polynor bornanes **124** and **125**, respectively (Scheme 19b).[35] The *exo,exo* stereoselectivity of such cycloadditions is typified by the CNC-[3]polynorbornane **126a**, the structure of which has been confirmed by X-ray crystallography.[36a]

These reactions, combined with the finding that the related 1,3-dipolar coupling of cyclobutene epoxides with 7-azabenzonorbornadienes also proceeds stereoselectively, opened the way to produce extended length *syn*-facial NN-[*n*]polynorbornanes and NO-[*n*]polynorbornanes and this is discussed in the next section.

A range of [3]polynorbornanes **128** containing methylene bridges, hetero-bridges as well as isopropylidene or cyclopropylidene derivatives are readily accessed by reaction of the appropriate bridge-modified benzonorbornadiene **80** with fused cyclobutanoaziridines **127**. As the central N-bridge in the series of [3]polynorbornanes **128** is flanked by various hetero or modified carbon bridges (Scheme 20), a crystallographic and ^{15}N spectroscopic study of bridge nitrogen geometry and invertomer properties is currently underway in our laboratories in collaboration with Dr John Malpass, Leicester University, UK.[36]



Scheme 19



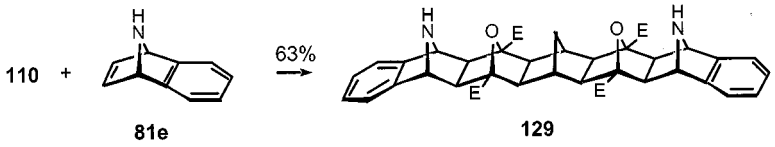
Scheme 20

6. Polarofacial Polynorbornanes (with G. Sun and P. Foley)

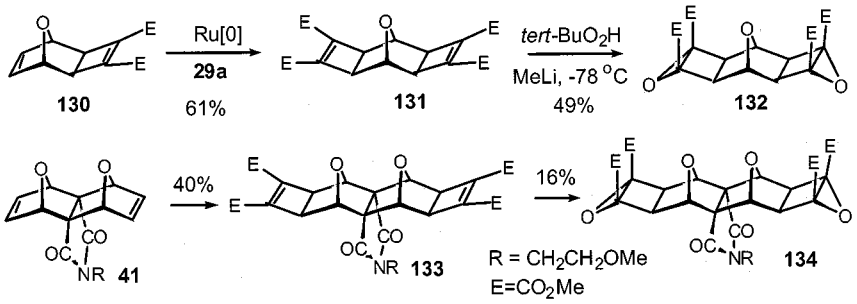
Taking this novel stereoselective coupling protocol into dual epoxide and dual aziridine cycloadditions, has allowed access to a unique range of all-oxygen bridged, all-nitrogen bridged and mixed nitrogen/oxygen bridged [*n*]polynorbornanes (Scheme 21). First, we established the credentials of the 1,3-dipolar cycloaddition reaction of a bis-epoxide to access hetero-bridged [5]polynorbornanes by thermally reacting the parent 7-azabenzonorbornadiene **(80e)** with bis-epoxide **110**, which affords the NOCON-[5]polynorbornadiene **129** in 63% yield.

This encouraging result led us to prepare bis-epoxides with oxygen bridges in the alicyclic framework. Formation of dual epoxides **132** (single O-bridge) and **134** (dual O-bridge) used a common two-step protocol which involved Mitsudo addition of dimethyl acetylenedicarboxylate **(29a)** with 7-oxanorbornenes **130** and **41** to produce bis-cyclobutene 1,2-diesters **131** and **133**, respectively, which are then subjected to nucleophilic epoxidation to afford the required bis-epoxides **132** and **134**, respectively (Scheme 22).

Efficient cycloaddition occurs between the bis-epoxide **132** and dienophile **80a** to provide access to the O^5-[5]polynorbornadiene **135** (Scheme 23). In this cycloaddition, a mixture of three isomers is obtained which differ in the stereochemistry of the fusion: the *syn*-facial O^5-[5]polynorbornadiene **135** (two *exo,exo* fusions), the cavity system **137** (C_{2v}-symmetry, two *exo,endo* fusions), and the less symmetrical O^5-[5]isopolynorbornadiene **136** (one *exo,exo*- plus one *exo,endo* fusion). These products were separated by column chromatography and their structures assigned on the basis of NMR spectroscopy. Attempts to prepare the O^6-[6]polynorbornadiene **138** are currently underway, but early results

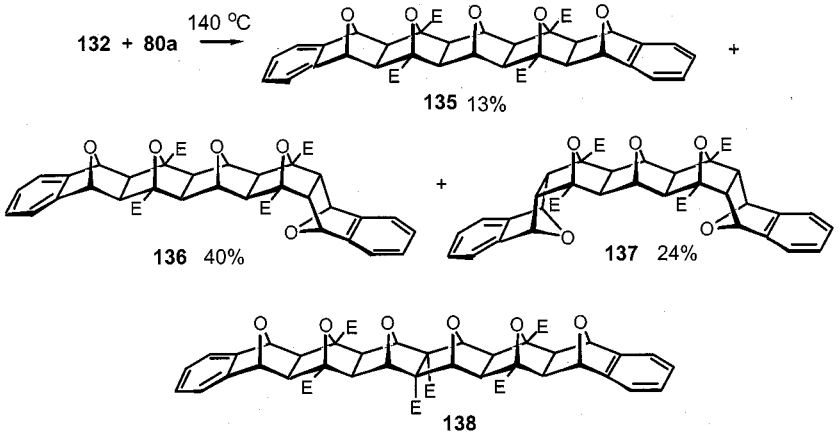


Scheme 21



130 131 132 41 133 134

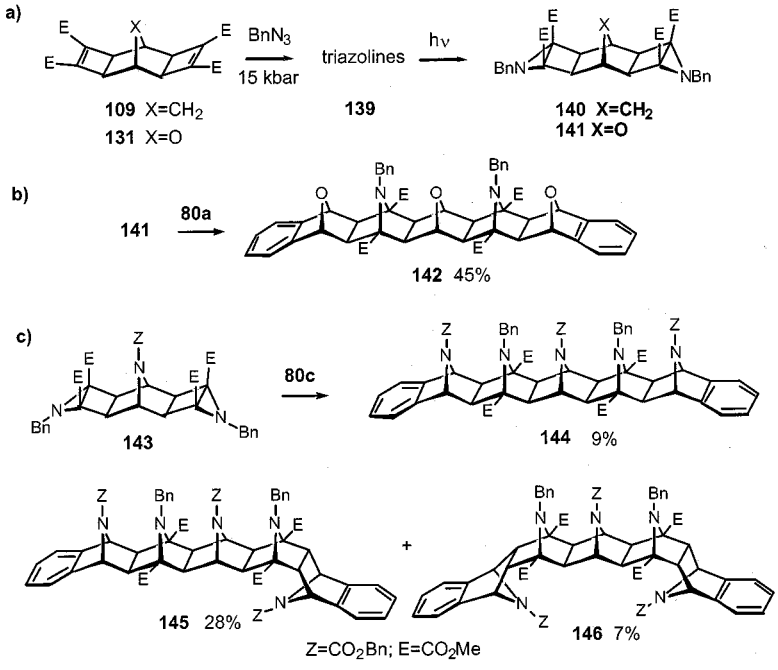
Scheme 22



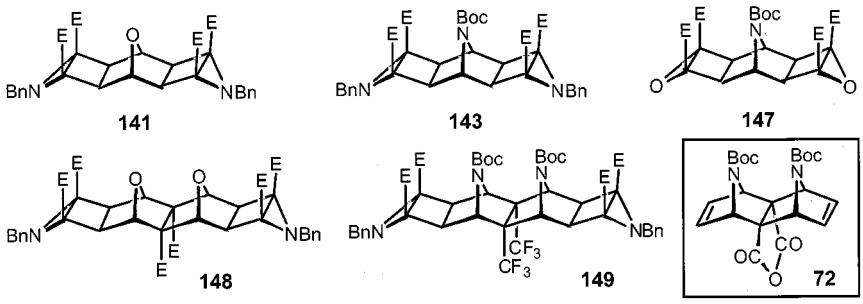
Scheme 23

suggest that the O^6-[6]isopolynorbornadienes dominate to the exclusion of the *syn*-facial isomer **138**.

For the production of N,O-bridged systems, we prepared the bis-aziridines **140** and **141** using the two-step process mentioned above (Scheme 19), except that we employed high pressure conditions (15 kbar) to enforce reaction[37] of benzyl azide to the bis-cyclobutene 1,2-diesters **109** and **131**, respectively (Scheme 24a). Again, expulsion of dinitrogen was achieved photochemically (benzene, 300 nm) from the mixture of σ- and Δ triazoline adducts **139** produced in each case. Similar conditions were used to prepare bis-aziridine **141** from **131** (Scheme 2).



Scheme 24



Scheme 25

The bis-aziridine **141** reacts with 7-oxabenzonorbornadiene **(80a)** to form a single product **142** in which there are five juxtaposed hetero-bridges (Scheme 24b). Dual coupling of bis-aziridine **143** with the *N*−Cbz-7-azabenzonorbornadiene **80c** opened access to the N^5[5]polynorbornadiene **144** and N^5-[5]isopolynorbornadienes **145**, **146**, the first systems in which all five bridges contain nitrogen (Scheme 24c).

The ^{1}H NMR spectra of compounds **144**−**146** are very complex at room temperature due to the invertomerisation of the *N*-benzyl substituents and the carbamate-type isomerisation of the *N*−Cbz groups.[38]

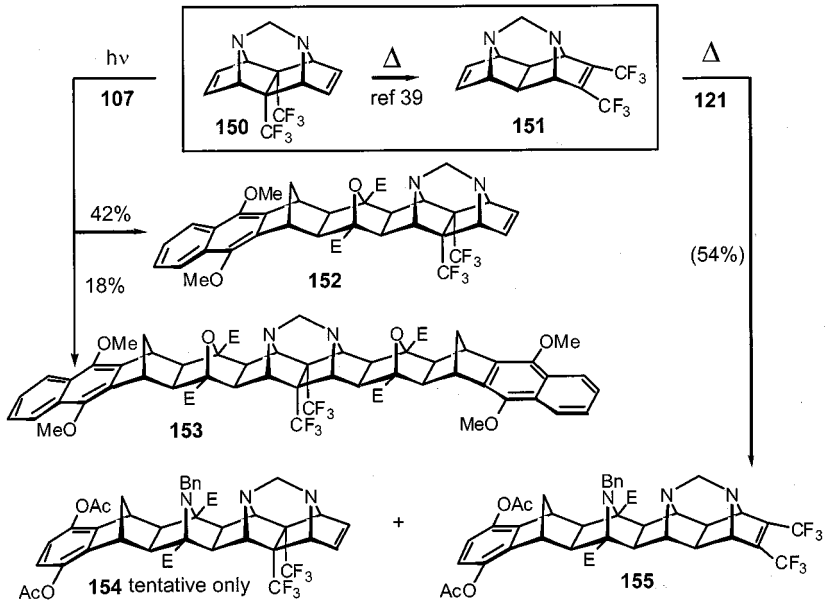
As the number and type of epoxide and aziridine block reagents grows, so the potential for preparing all nitrogen and other heteroatom systems with five or more bridges becomes a realistic goal. The dual 1,3-dipolar precursor blocks shown in Scheme 25 have been prepared (**149** still to be confirmed), and their coupling potential with dual alkene blocks such as **72**, is currently being explored.

7. Bridge-Bridge Linked Polynorbornanes (with M. R. Johnston and D. Margetic)

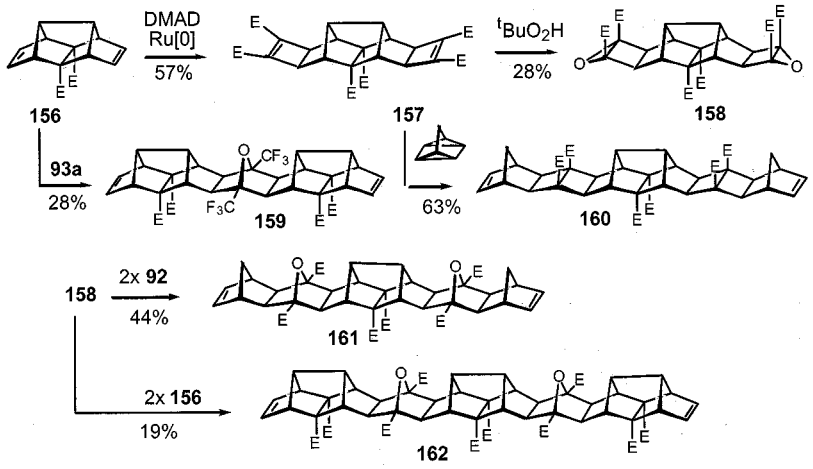
As part of our molecular architecture program, we investigated the role of sesquinorbornadiene **150**[39] as an alkeneblock, since [*n*]polynorbornanes derived from it offer a less-curved frame than regular [*n*]polynorbornanes (see next section). All attempts to add cyclic 1,3-dienes to **150** were unsuccessful under thermal or high pressure conditions; in addition, thermal 1,3-dipolar and 1,3,4-oxadiazole reactions failed to yield adducts with **150**.

The value of the photochemical variant of the 1,3-dipolar reaction was demonstrated in this context when it was found that reaction of light-absorbing epoxide **107** with sesquinorbornadiene **150** yields both the 1:1 adduct **152** and the 2:1 adduct **153** (Scheme 26).

Aziridine-based 1,3-dipolar coupling was also valuable, but to a lesser extent, as heating **150** with aziridine **121** yields the coupled product **155** derived from the isomeric alkene **151**, a known thermal rearrangement product from



Scheme 26



Scheme 27

150 (Scheme 26).[39] There was some evidence for the presence of the unrearranged adduct **154** in the crude reaction mixture (alkene protons at $\delta = 6.1$), but this is a minor product and could not be separated in pure form.

A particularly disappointing aspect of the chemistry of **150** is its failure to undergo Mitsudo coupling with dimethyl acetylenedicarboxylate to form a [2 + 2] cycloadduct. This recalcitrance stands in stark contrast with the σ-linked sesquinorbornadiene **156**.[40] A whole range of rods has been prepared[41] starting from bis-alkene **156** and some of these results are summarised in Scheme 27. A feature of these compounds is that incorporation of the σ-bridge changes the topology of the scaffold frame from being curved, which is characteristic of [*n*]polynorbornanes, to being rod-like (see Modelling, next section).

The synthesis of cyclobutene epoxides (or related aziridines) such as **158** was readily achieved via the intermediate formation of bis(cyclobutene-1,2-diester) **157**. The bis-alkene **156** also undergoes 1,3,4-oxadiazole coupling to furnish **159**, while cycloaddition of quadricyclane to the cyclobutene π centres in **157** provides entry to the elongated bis-alkene **160**. Double 1,3-dipolar coupling of the bis-epoxide **158** with norbornadiene **92** to form spacer **161**, or with excess **156** to form the elongated spacer **162**, further shows the versatility available in this series and these features are currently being exploited in assembly chemistry.[42]

8. Molecular Modelling of Polynorbornanes and Related Molracs (with D. Margetic)

a) Heteropolynorbornanes with Arc-Shaped Topology

The hypothetical [9]polynorbornane **163**, composed entirely of fused bicyclo[2.2.1]heptane units, was taken as the reference point for the modelling; inspection of the modelled structure (Figure 4) indicated that it had adopted a curved topology. The steric interaction between the protons in juxtaposed methylene bridges contribute to the pronounced arc-shape forced on the molecule.

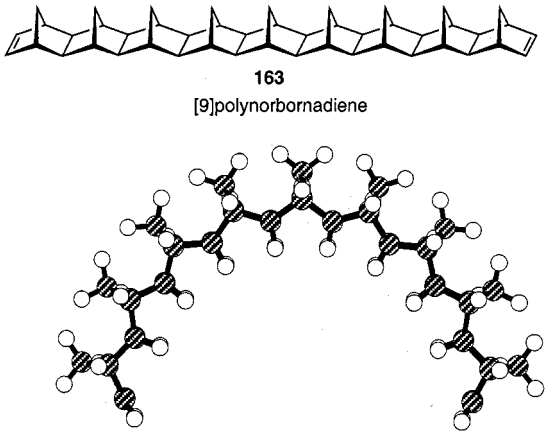


Figure 4. Molecular modelled (AM1) structure for [9]polynorbornadiene **163**

Replacement of all the methylene bridges with nitrogen bridges removes some of the steric interaction associated with the bridge protons, yet there is still crowding associated with the *N*-substituents and the N^9-[9]polynorbornane **164** retains most of the curvature found in **163**. With the O^9-[9]polynorbornane **165**, composed of 7-oxanorbornane units, the steric interaction between the adjoining O-bridges is essentially removed and this is reflected in the significant straightening of the arc-shape topology (for diagrams, see ref.[3b]). At this point in time, these parental systems are still chemical curiosities, since they have not been synthesised, although we have made significant progress in systems containing additional bridgehead ester substituents on the frame. We have already succeeded in fusing five 7-azanorbornane rings together in the (NZ,NBn,NZ,NBn,NZ-[5]polynorbornane **144** (see Scheme 24), six 7-oxanorbornanes rings in O^6-[6]polynorbornane **138** (see Scheme 23) and nine bicyclic rings in the $(CO)^4$C-[9]polynorbornane system **167** (Figure 5).[42] Compounds containing effector groups fused at the termini of **167** form V-shaped cavity systems

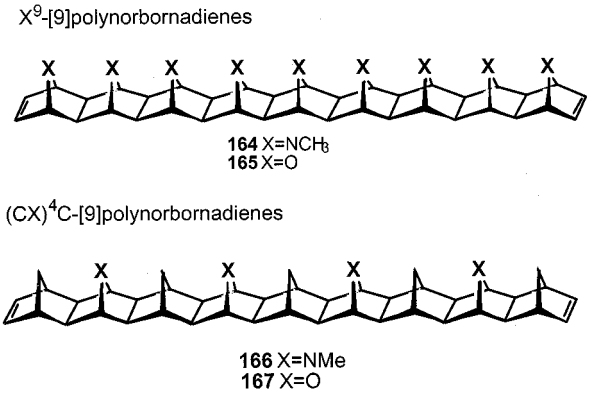


Figure 5. Representative hetero-bridged [9]polynorbornanes

owing to the curvature of the polynorbornane frame (see ref.[43] for details of the modelled topology).

In the hemi-nitrogen series, the $(CN)^4$C-[9]polynorbornadiene **166** retains almost the same curvature as the all-carbon C^9-[9]polynorbornane **163**. As a direct consequence of this degree of curvature, the terminal π bonds in **166** are directed inwards and attachment of functional units to these terminal positions should provide convergently orientated systems, whereas in the corresponding hemi-oxygen system, $(CO)^4$C-[9]polynorbornadiene **167** would have similar substituents approaching a parallel orientation. We are yet to establish the role that the *N*-substituent has to play on the degree of curvature of the polynorbornane frame, but it is conceivable that such substituents could be used to fine-tune the topology.

b) Approaches to Straightening out the Curves

Three separate methods have been developed to form rod-like spacer systems. The first of these was to replace alternative norbornane subunits in the [*n*]polynorbornane with bicyclo[2.2.0]hexanes to produce [*n*]norpolynorbornanes; the second was to invert sections of the norbornane frame such that the curvatures were opposed; the final − and most practical − has been to retain all the norbornane units, but to link some of the adjoining norbornane methylene bridges by a σ bond.

Significant changes in topology occur as the norbornane subunits in [*n*]polynorbornanes are replaced with bicyclo-[2.2.0]hexane subunits to form nor [*n*]polynorbornanes. Such systems have found wide use as spacers and scaffolds following our report of their synthesis in 1983.[43] Molecular modelling demonstrated that the frame in the bis-nor-C^5-[5]polynorbornadiene **168** is considerably less curved (Figure 6) than the C^9-[9]polynorbornadiene **163** (Figure 4). The modelling prediction for geometry of **168** is supported by X-ray structure analysis of the tetramethoxycarbonyl derivative **169**.[45] We have since studied [*n*]ladderanes where there are only cyclobutane rings fused together and the resultant molecular frame is rod-like in shape, e.g. [10]ladderane **170** (Figure 6). The synthesis of such [*n*]ladderanes was achieved by a variant of our tandem cycloaddition protocol developed for molrac synthesis.[46] In the [*n*]ladderane synthesis, the ruthenium-catalysed addition is retained to form the cyclobutene 1,2-diester, but applied to the unsubstituted cyclobutene π bond arising from the addition of cyclobutadiene to the terminal cyclobutene 1,2-diester.

The use of sinusoidal topology was employed in our approach to molrac spacers with terminal *cisoid* alcohols.[46] Cyclobutenomaleimide **174** was prepared from *tert*-butoxyquadricyclane **(171)** by thermal addition of *N*-methyl-3,4-dibromomaleimide **(172)** to yield a mixture of stereoisomeric bromo adducts **173** (not separated) which were debrominated (Zn/Ag couple) to yield the highly dienophilic cyclobutenomaleimide **174** (Scheme 28). A key feature of the reaction of **174** with cyclopentadiene **(22)** is that it produces the Diels−Alder adduct **175** in high yield, thereby placing the new norbornene subunit on the underface of the product. While **175** contains two norbornene subunits, the reactivities of the π bonds are quite distinct, owing to the *exo*-face screening of one π-centre by the *syn*-positioned *tert*-butoxy group. Thus, treatment of **175** with 1,3,4-oxadiazole **93a** affords the coupled product **176** in a process that is both site-selective and stereoselective. Molecular modelling confirmed the overall flattening of the frame in product **176** as the curvature of the subunits compensate each other (Figure 7).

While this double curve technique was applicable to the formation of the protected spacer diol **176**, it lacked general application to spacer chemistry. A solution to this problem was forthcoming when molecular modelling confirmed that the introduction of a σ bond between the methylene bridges of sesquinorbornane significantly reduces the interbridge distance and flattens out the carbon framework. This effect is illustrated by the change in topology of the arc-shaped [8]polynorbornane **178** relative to the molecular rod **177** (Figure 8) where three such σ-linkages have been introduced into the frame. The importance of this finding at-

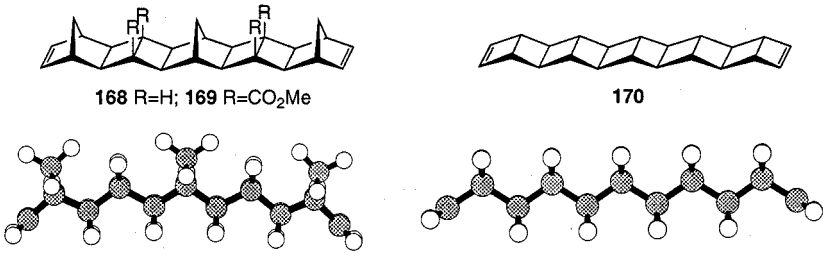
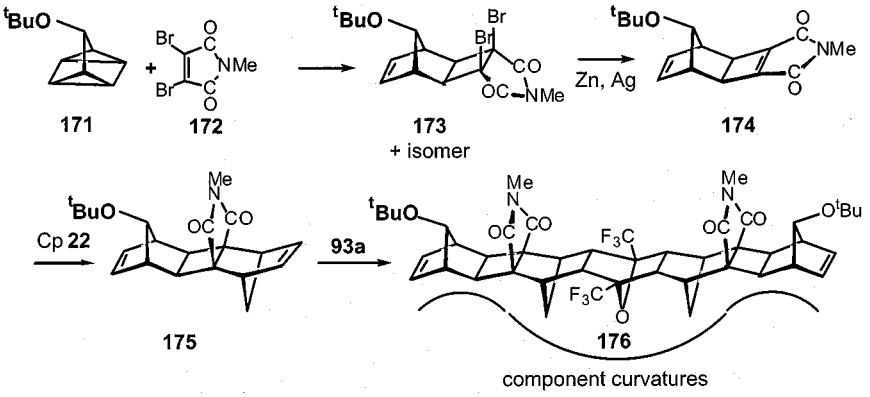


Figure 6. Modelled structures (AM1) for bis-nor-C^5-[5]polynorbornadiene **168** and [10]ladderane **170**



Scheme 28

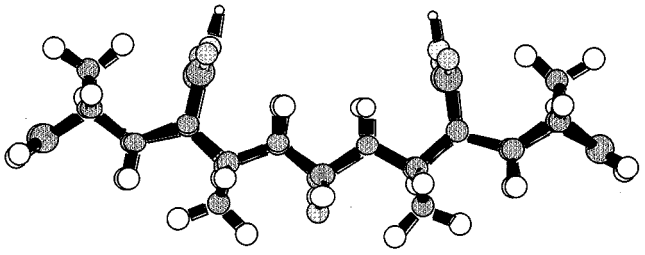


Figure 7. Molecular modelled (AM1) structure of a simplified version of **176** in which the *O*-and *N*-substituents and the CF_3 groups have been removed.

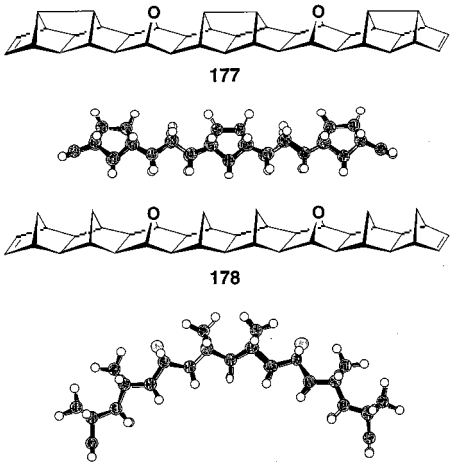


Figure 8. Modelled structures (AM1) for σ-linked polynorbornane **177** and the regular $C^2OC^2OC^2$-[8]polynorbornane **178**

tained immediate credence as a substituted member of this ring system has already been prepared − see [8]polynorbornane **162** (Scheme 27).

9. Conclusion

[*n*]Polynorbornanes are a unique class of molecules that are elegantly suited for the development of new architectures. They offer a distinctive curved topology which can be fine-tuned by variation of the heterobridges and their σ-linked counterparts to provide rod-like frames. Significant advances have already been made over the last 2−3 years in the synthesis of hetero-bridged [*n*]polynorbornanes as a result of the 1,3-dipolar coupling techniques. Already [*n*]polynorbornanes containing up to nine fused norbornane-type rings have been prepared in the CO-series and new blocks are now in hand which should allow others of this length to be prepared in the N,N and N,O series. Advances in the N-bridged arena have been strengthened by access to high pressure and the stage is now set for the production of new molecular architectures based on the hetero[*n*]polynorbornane frames.

As functionality can be linked to such frames, it is possible to custom-design and build structures capable of providing new geometric inter-relationships between the separated functionality. The [*n*]polynorbornanes are no longer chemical curiosities as the groundwork has now been completed for their synthesis using lego-type building blocks. Already we have programs based on the use of framework molecules composed of functionalised [*n*]polynorbornane for research into nanotechnology, bis-intercalator anticancer molecules, energy and electron transfer, self assembly systems, and we consider that they also have potential in the production of new materials and in host/guest chemistry.

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[1] [1a] J. M. Lehn, *Supramolecular Chemistry-Concepts and Perspectives*, VCH, Weinheim, **1995**. − [1b] J. K. M. Sanders, *Chem. Eur J.* **1998**, *4*, 1378−1383. − [1c] J. Rebek, *Acc. Chem. Res.* **1999**, 32, 278−286

[2] M. R. Johnston, M. J. Gunter, R. N. Warrener, *Chem. Commun.* **1998**, 2739−2740.

[3] [3a] R. N. Warrener, D. N. Butler, R. A. Russell, *Synlett* **1998**, 566−573. − [3b] R. N. Warrener, D. Margetic, G. Sun, A. S.

Amarasekara, P. Foley, D. N. Butler, R. A. Russell, *Tetrahedron Lett.* **1999**, *40*, 4111−4114.
[4] R. N. Warrener, G. M. Elsey, L. Maksimovic, M. R. Johnston, C. H. L. Kennard, *Tetrahedron Lett.* **1995**, *36*, 7753−7756.
[5] G. Sun, D. N. Butler, R. N. Warrener, D. Margetic, J. R. Malpass, Article 062, *Electronic Conference on Heterocyclic Chemistry '98''* **1998**, (Eds.: H. S. Rzepa, O. Kappe), Imperial College Press, http://www.ch.ic.ac.uk/ectoc/echet98/.
[6] J. D. Slee, E. LeGoff, *J. Org. Chem.* **1970**, *35*, 3897−3901.
[7] [7a] A. W. McCulloch, D. G. Smith, A. G. McInnes, *Can. J. Chem.* **1973**, *51*, 4125−4136. − [7b] G. Weber, K. Menke, H. Hopf, *Chem. Ber.* **1980**, *113*, 531−541.
[8] O. Diels, K. Alder, *Justus Liebigs Ann. Chem.* **1931**, *490*, 243−257.
[9] J. Kallos, P. Deslongchamps, *Can. J. Chem.* **1962**, *44*, 1239−1245.
[10] M. Lautens, E. Fillion, *J. Org. Chem.* **1996**, *61,* 7994−7995.
[11] [11a] P. D. Bartlett, G. L. Combs, Jr., A.-K., T. Le, W. H. Watson, J. Galloy, M. Kimura, *J. Am. Chem. Soc.* **1982**, *104*, 3131−3138. − [11b] P. D. Bartlett, A. J. Blakeney, W. H. Watson, M. Kimura, *J. Am. Chem. Soc.* **1980**, *102*, 1383−1390. − [11c] J. R. Edman, H. E. Simmons, *J. Org. Chem.* **1968**, *35*, 3808−3816.
[12] R. N. Warrener, A. C. Schultz, D. N. Butler, S. Wang, I. B. Mahadevan, R. A. Russell, *J. Chem. Soc*., *Chem. Commun.* **1997**, 1023−1024.
[13] M. N. Paddon-Row, E. Cotsaris, H. K. Patney, *Tetrahedron* **1986**, *42*, 1779−1788.
[14] [14a]J. K. Stille, D. A. Frey, *J. Am. Chem. Soc.* **1959**, *81*, 4273−4275. − [14b] A. P. Marchand, J. E. Rose, *J. Am. Chem. Soc.* **1968**, *90*, 3724−3731. − [14c] J. Mantzaris, E. Weissberger, *J. Org. Chem.* **1974**, *39*, 726−728.
[15] [15a] R. A. Russell, R. N. Warrener, R. W. Longmore, K. D. V. Weerasuria, *Aust. J. Chem.* **1991**, *44*, 1341−1345. − [15b] R. N. Warrener, L. Maksimovic, I. G. Pitt, I. Mahadevan, R. A. Russell, E. R. T. Tiekink, *Tetrahedron Lett.* **1996**, *37*, 3773−3776.
[16] R. N. Warrener, S. Wang, L. Maksimovic, P. M. Tepperman, D. N. Butler, *Tetrahedron Lett.* **1995**, *36*, 6141−6144.
[17] R. N. Warrener, S. Wang, R. A. Russell, M. J. Gunter, *Synlett* **1997**, 47−50.
[18] R. V. Williams, C.-L. A. Sung, H. A. Kurtz, T. M. Harris, *Tetrahedron Lett*. **1988**, *29*, 19−20.
[19] D. N. Butler, D. Margetic, R. N. Warrener, *Synlett* **1999**, submitted for publication.
[20] R. N. Warrener, I. G. Pitt, R. A. Russell, *Aust. J. Chem.* **1991**, *43*, 1293−1305.
[21] D. N. Butler, D. Margetic, P. J. C. O'Neill, R. N. Warrener, *Synlett* **2000**, *10*, 98−101.
[22] D. J. Cram, C. S. Montgomery, G. R. Knox, *J. Am. Chem. Soc.* **1966**, *88*, 515−525.
[23] [23a] M. Lautens, E. Fillion, *J. Org. Chem.* **1997**, *62,* 4418−4427. − [23b] M. Lautens, E. Fillion, *J. Org. Chem.* **1998**, *63,* 647−656.
[24] D. N. Butler, J. R. Malpass, D. Margetic, R. A. Russell, G. Sun, R. N. Warrener, *Synlett* **1998**, 588−589.
[25] [25a] Z. Chen, M. L. Trudell, *Chem. Rev.* **1996**, *96*, 1179−1193. − [25b] M. G. B. Drew, A. V. George, N. S. Isaacs, H. S. Rzepa, *J. Chem. Soc., Perkin Trans. 1* **1985**, 1277−1284.
[26] T. Sasaki, T. Manabe, S. Nishida, *J. Org. Chem.* **1980**, 476−479.
[27] L. F. Fieser, M. J. Haddadin, *Can. J. Chem.* **1965**, *43*, 1599−1606.
[28] D. Belkacemi, J. W. Davies, J. R. Malpass, A. Naylor, C. R. Smith, *Tetrahedron* **1992**, *48*, 10161−10176.
[29] [29a] D. Margetic, J. R. Malpass, R. N. Warrener, Article 15, ECCC5 "Electronic Computational Chemistry'' Conference **1998**, http://www.hackberry.chem.niu.edu/ECCC5. − [29b] D. Margetic, R. N. Warrener, J. R. Malpass, *Fifth Electronic Conference on Computational Chemistry* **1998**, (Ed.: S. Bachrach).
[30] [30a] N. V. Vasiliev, Yu. E. Lyashenko, M. V. Galakhov, A. F. Kolomiets, A. F. Goutar, G. A. Sokolskii, *Khim. Geterotsikl Soedin*. **1990**, 95−100. − [30b] N. V. Vasiliev, Y. E. Lyashenko, A. E. Patalakha, G. A. Sokolskii, *Fluorine Chem.* **1993**, *65*, 227−231.
[31] [31a] G. Seitz, H. Waβmuth, *Chemiker Zeitung* **1988**, *112*, 80−81. − [31b] G. Seitz, Ch. Gerninghaus, *Pharmazie* **1994**, *49*, 102−106.
[32] F. Thalhammer, U. Wallfahrer, J. Sauer, *Tetrahedron Lett.* **1988**, *29*, 3231−3234.
[33] R. N. Warrener, D. Margetic, E. R. T. Tiekink, R. A. Russell, *Synlett* **1997**, 196−198.
[34] [34a] T. Mitsudo, H. Naruse, T. Kondo, Y. Ozaki, Y. Watanabe, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 580−581. − [34b] T. Mitsudo, K. Kokuryo, T. Shinsugi, Y. Nakagawa, Y. Watanabe, Y. Takegami, *J. Org. Chem.* **1979**, *44*, 4492−4496.
[35] R. N. Warrener, D. N. Butler, R. A. Russell, D. Margetic, M. Hammond **1998**, unpublished results.
[36] [36a] J. R. Malpass, D. N. Butler, M. R. Johnston, M. L. A. Hammond, R. N. Warrener, *Org. Lett.* **2000**, *2*, 724−728. − [36b] D. N. Butler, M. L. A. Hammond, M. R. Johnston, G. Sun, J. R. Malpass, J. Fawcett, R. N. Warrener, *Org. Lett.* **2000**, *2*, 721−724.
[37] G. T. Anderson, J. R. Henry, S. M. Weinreb, *J. Org. Chem.* **1991**, *56*, 6946−6948.
[38] [38a]A. M. Belostotskii, H. E. Gottlieb, A. Hassner, *J. Am. Chem. Soc.* **1996**, *118*, 7783−7789. − [38b] D. Belkacemi, J. R. Malpass, *Tetrahedron* **1993**, *49*, 9105−9116. − [38c] J. W. Davies, M. L. Durrant, M. P. Walker, D. Belkacemi, J. R. Malpass, *Tetrahedron* **1992**, *48*, 861−884 and references cited therein.
[39] M. Visnick, M. Battiste, *J. Chem. Soc., Chem. Commun.* **1985**, 1621−1622.
[40] [40a] L. A. Paquette, J. C. Weber, T. Kobayashi, Y. Miyahara, *Org. Syn.* **1989**, *68*, 198−205. − [40b] R. Bartetzko, R. Gleiter, J. L. Muthardt, L. A. Paquette, *J. Am. Chem. Soc.* **1978**, *100*, 5589−5594. − [40c] L. A. Paquette, M. J. Wyvratt, I. I. C. Berk, R. E. Moerck, *J. Am. Chem. Soc.* **1978**, *100*, 5845−5855.
[41] D. Margetic, M. R. Johnston, E. R. T. Tiekink, R. N. Warrener, *Tetrahedron Lett.* **1998**, *39*, 5277−5280.
[42] A. C. Schultz, L. S. Kelso, M. R. Johnston, D. Margetic, R. N. Warrener, F. R. Keene, *Inorg. Chem.* **1999**, *38,* 4906−4909.
[43] R. N. Warrener, D. Margetic, A. S. Amarasekara, R. A. Russell, *Org. Lett.* **1999**, *1,*1999−202
[44] R. N. Warrener, I. G. Pitt, D. N. Butler, *J. Chem. Soc., Chem. Commun.* **1983**, 1340−1342
[45] R. N. Warrener, C. H. L. Kennard*,* **1996**, unpublished results
[46] X-ray structure available as supplementary material in R. N. Warrener, G. Abbenante, C. H. L. Kennard, *J. Am. Chem. Soc.* **1994**, *116*, 3645−3646.
[47] R. N. Warrener, P. Groundwater, I. G. Pitt, D. N. Butler, R. A. Russell, *Tetrahedron Lett.* **1991**, *32*, 1885−1888.

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