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syn-Facial hetero-bridged [*n*]polynorbornanes: a new class of polarofacial framework molecules composed of fused 7-oxa- and 7-azanorbornanes

Ronald N. Warrener,[a,*] Davor Margetic,[a] Patrick J. Foley,[a] Douglas N. Butler,[a] Alain Winling,[b] Kerry A. Beales[b] and Richard A. Russell[b,*]

[a]*Centre for Molecular Architecture, Central Queensland University, Rockhampton, Queensland 4702, Australia*
[b]*Centre for Chiral and Molecular Technologies, Deakin University, Geelong, Victoria 3217, Australia*

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Abstract—New oxygen-bridged norbornane-fused cyclobutene epoxides and bis-(cyclobutene epoxides) are described and shown to react stereoselectively with 7-azanorbornenes to produce *syn*-facial *N*,*O*-bridged polynorbornanes and stereorandomly with 7-oxanorbornenes to produce *O*,*O*-bridged polynorbornanes as mixtures of *syn*-facial and *anti*-facial products.[1] Polarofacial systems containing up to six *syn*-facial norbornane bridges are described, while systems with seven co-facial oxygen atoms have been prepared by incorporating terminal epoxide rings to O^5-[5]polynorbornanes. Ester-substituted 1,3,4-oxadiazoles are shown to be useful reagents for coupling 7-oxanorbornanes and produce predominantly *syn*-facial *O*-bridged polarofacial systems together with their *anti*-facial isomers.

1. Introduction

We have been interested in the preparation of bridged polarofacial systems of type **1** (Fig. 1) where the *syn*-facial orientation of the oxa-bridge and aza-bridges provide the polar face.[2,3] Such compounds are a new type of polarofacial molecule and have potential in a variety of chemical areas, e.g. their polarofacial properties might be exploited as micelle components, surfactants or ion channel agents, their *syn*-facial bridges as models for the study of proximate heteroatom interactions, especially through space, and the unique opportunities offered for juxtaposed NH-bridged systems for intermolecular assembly through H-bonding or metal complexation.

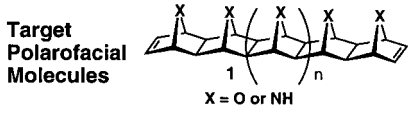
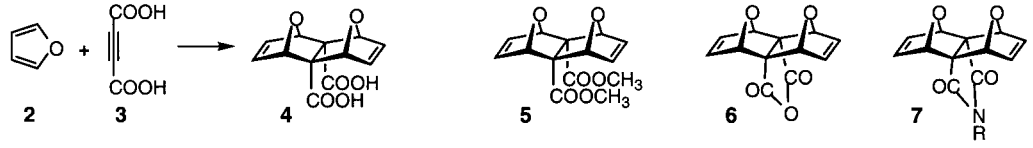


Figure 1.

In one of the original reports in 1931 by Diels and Alder on their now famous reaction,[4] they described the production of the first *syn*-facial O^2-[2]polynorbornane **4**† by the reaction of furan **2** with acetylenedicarboxylic acid **3**, although it was left to others to confirm the stereochemistry.[5] Compound **4** has been used subsequently as a source of *syn*-facial polynorbornane products **5**–**7**, some of which are used as building BLOCKs in this and earlier studies (Scheme 1).[6]



Scheme 1.

Keywords: cycloadditions; epoxides; mechanisms; polycyclic aliphatic compounds; 1,3,4-oxadiazoles.

* Corresponding authors. Tel.:+7-4930-9845; fax: +7-4930-9917; e-mail: r.warrener@cqu.edu.au

† **Footnote on nomenclature**. The number of norbornane units in the system is designated in square brackets as a prefix, e.g. [*n*]polynorbornane. The type of hetero-bridges in that particular compound is designated by a capitalised prefix, listing in order the heteroatom involved and separated from the [*n*] designator by a hyphen, e.g. O_3-[3]polynorbornane **27**, NO_3N-[5]polynorbornane **55**. In this context, a carbon bridge is designated by C and dealt with in the same way as the heteroatoms, e.g. CO^2-[3]polynorbornane **22**. The stereochemistry of the bridges are not designated specifically, except that the system in which all the bridges are on the same face is designated as *syn*-facial, while all other isomers are referred to as *anti*-facial products.

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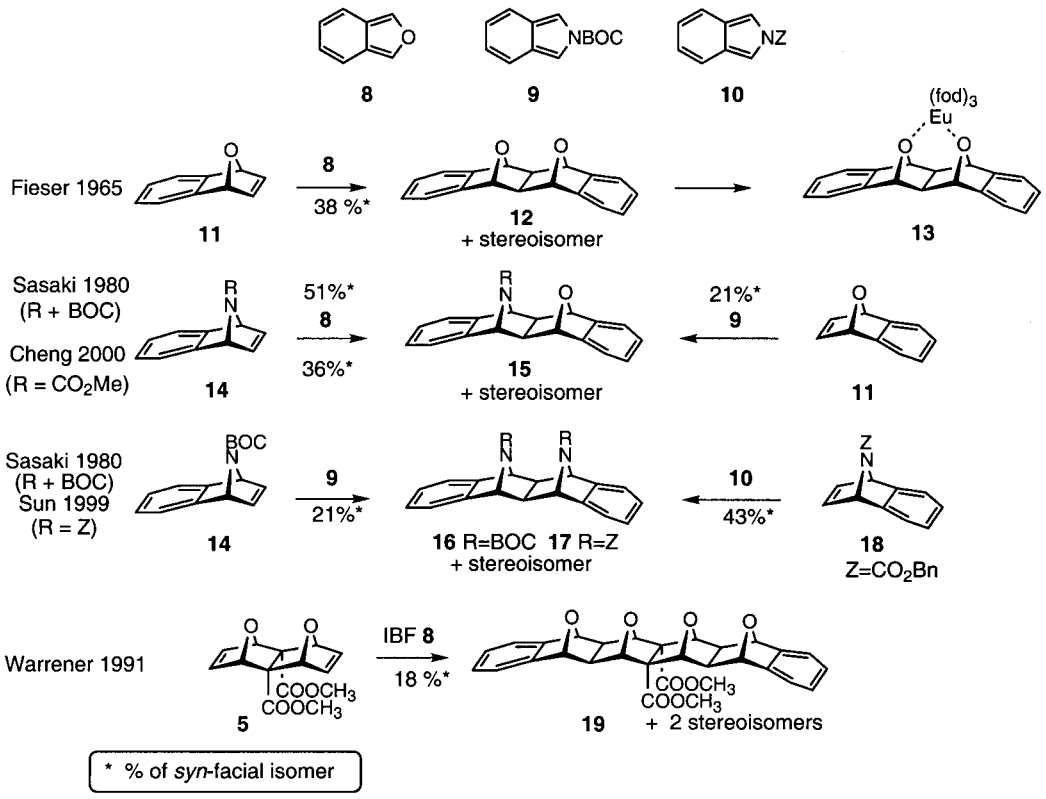


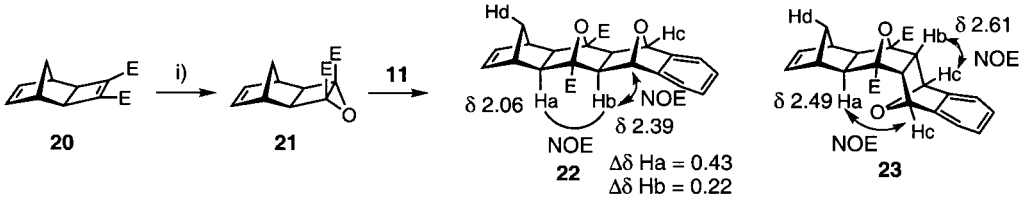
Scheme 2.

Some time later Fieser and Haddadin reported[7] that the dibenzo-derivative of the parent *syn*-facial dioxasesquinorbornadienes could be formed by reaction of isobenzofuran **8** with 7-oxabenzonorbornadiene **11**; a mixture of two stereoisomeric 1:1-adducts was produced including a significant proportion of the *syn*-facial adduct, O^2-[2]polynorbornane **12** (Scheme 2). We later demonstrated the ligand potential of **12** through complexation with $Eu(fod)_3$ to form **13**.[8] In a more comprehensive synthetic study, Sasaki and his coworkers described access to similar *syn*-facial NO-[2]polynorbornanes containing an oxygen-bridge adjacent to a nitrogen bridge, e.g. **15**, either through the addition of isobenzofuran **8** to *N*–BOC-7-azabenzonorbornadiene **14** or by addition of *N*–BOC-isoindole **9** to 7-oxabenzonorbornadiene **11**.[9] A report just at hand, describes the addition of isobenzofuran to *N*-methoxycarbonyl-7-azabenzonorbornadiene.[10] Further, the addition of *N*–BOC-isoindole **9** to the 7-azabenzonorbornadiene **14** furnished the first example of the dual nitrogen bridged system, N^2-[2]polynorbornane **16**, albeit in only moderate yield (21%).[11] We have since found that the yield of the *syn*-facial product of this type can be doubled using the *N-Z* derivatives, **10** and **18**, which form **17** in 43% yield.[11] Our group approached the synthesis of *syn*-facial O^3-[3]polynorbornanes, the first of the higher-order systems, using the coupling of 7-oxabenzonorbornadienes, e.g. **11**, with 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole but found in these initial studies that only products with *anti*-facial oxygen bridges were formed, however we now know that *syn*-facial products can be formed from some 7-oxanorbornene substrates. An updated study using ester-substituted 1,3,4-oxadiazoles is reported herein and shown to be much more successful in achieving the synthesis of *syn*-facial O^3-[3]polynorbornanes. The longest *syn*-facial O^n[*n*]polynorbornane reported at the time our study commenced, was the tetra-bridged system **19** containing four oxygen bridges, formed by the addition of isobenzofuran **8** to the O^2-[2]polynorbornadiene **5**, however it was produced as a mixture with two other stereoisomers.[2,12]

2. Results and discussion

2.1. 1,3-Dipolar cycloadditions

All the Diels–Alder and 1,3,4-oxadiazole approaches to [*n*]polynorbornane synthesis described above, invariably gave stereoisomeric mixtures, so we sought a more stereoselective approach to the synthesis of hetero-bridged [*n*]polynorbornanes. We were attracted to the 1,3-dipolar cycloaddition route involving the 'LEGO' BLOCK coupling of norbornenes with cyclobutene epoxides (ACE coupling), since it is known to be highly stereoselective in its reaction with a range of norbornene dipolarophiles.[13] This ACE reaction involves the coupling of cyclobutene epoxides (via their ring-opened 1,3-dipole or 1,3-diradical) with norbornenes to form *syn*-facial cycloadducts which, when the cyclobutene epoxide is fused to a norbornene or a 7-heteronorbornene, produces a *syn*-facial [*n*]polynorbornane containing one or more oxygen-bridges. In a recent study,[14] we established that bis-(cyclobutene epoxides) can be employed, thereby opening the way to produce substantially longer [*n*]polynorbornanes than were presently available. Indeed, a whole range of CO-[*n*]polynorbornanes, including the 9-bridged system $(CO)^4$C-[9]polynorbornane, have been produced recently using this technique. We now report that hetero-bridged norbornenes can participate as

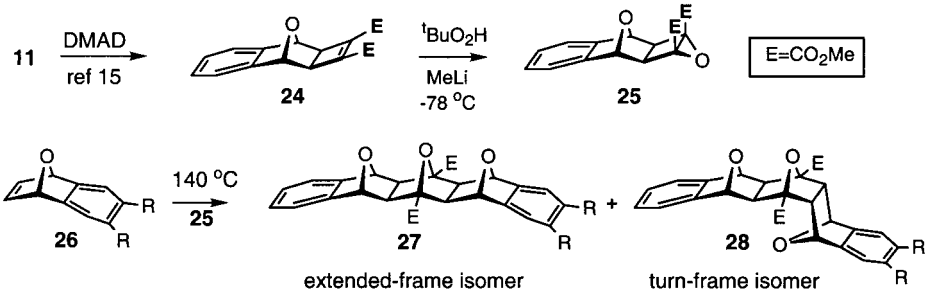


Scheme 3. (i) ^{t}BuOOH, MeLi, −78°C, E=CO_2Me.

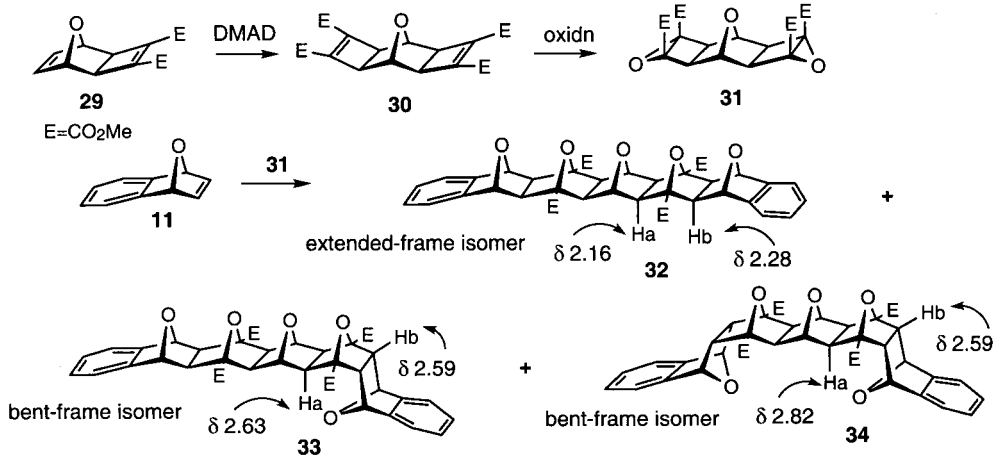
dipolarophiles in the ACE reaction thereby offering a direct route to hetero-bridged [*n*]polynorbornanes. In particular, 7-azanorbornenes produce *syn*-facial products almost exclusively, however, this stereoselectivity drops off when 7-oxanorbornenes are used as dipolarophiles.

The ACE reaction of cyclobutene epoxide **21** with 7-oxabenzonorbornadiene **11** produced two isomeric adducts **22** and **23** in a 7:5 ratio. These were distinguished by ^{1}H NMR spectroscopy where the *syn*-facial isomer **22** exhibited a NOE between protons Ha and Hb. The assignments for Ha and Hb in each isomer were made on a combination of long-range W-couplings which caused a broadening of the Ha resonance compared with Hb, and an NOE between Hb and the very sharp and characteristically downfield-shifted oxabridgehead proton Hc (Scheme 3). Both Ha and Hb exhibit an NOE with Hc in isomer **23**, a phenomena explained by the turn-frame geometry in which molecular modelling predicts a Ha–Hc distance of 2.71 Å and a Hb–Hc separation for 2.73 Å. Interestingly, the chemical shifts of protons Ha and Hb in **23** are downfield-shifted by 0.43 and 0.22 ppm respectively from their counterparts in **22**. We attribute this to a field effect from the oxygen atoms and note that such shifts are even more pronounced in CO-[*n*]polynorbornanes in which the *syn*-related methylene proton of the bridge is downfield-shifted in excess of 1.5 ppm. In these cases, the proton is in the same plane as the O-bridge and much closed through space.

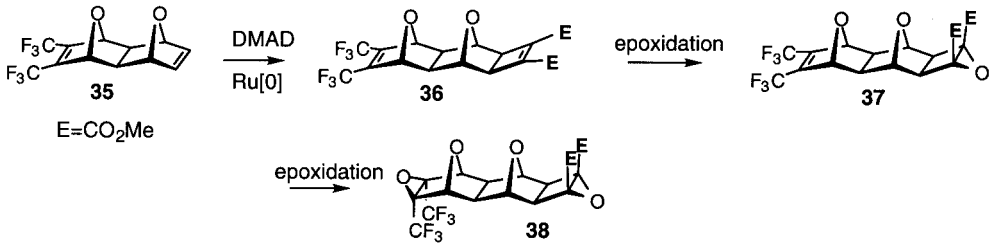
Incorporation of an oxa-bridge into the cyclobutene epoxide reagent caused no further loss of stereochemical integrity so that reaction of cyclobutene epoxide **25** (Scheme 4) with the 7-oxa benzonorbornadiene **11**(=**26a**) yielded the *syn*-facial adduct **27a** where there are three juxtaposed oxygen bridges, together with the *anti*-facial stereoisomer **28a**. A similar reaction between **25** and the dibromo-containing dipolarophile **26b** gave **27b** (46%) and **28b** (48%). As these reactions give roughly equal amounts of the two isomers and because these could be readily separated by chromatography (polarofacial isomers are less mobile), we have further explored this ACE approach for the synthesis of stretched variants.



Scheme 4. Series (a) R=H; Series (b) R=Br.



Scheme 5.



Scheme 6.

The oxa-bridged bis-epoxide **31** was specially prepared for this project by epoxidising the bis-cyclobutene-1,2-diester **30**. Double ACE coupling of **31** with 7-oxabenzo norbornadiene **11** afforded three products: the *syn*-facial product **32** (21%) with five juxtaposed oxygen bridges (Scheme 5), the *anti*-facial isomer **33** (56%) and the cavity system **34** (23%). The structure of each of these products was assigned by a combination of symmetry and chemical shift data for protons Ha and Hb.

Diagnostically, protons Ha and Hb in the C2v-symmetrical isomer **32** are at higher field than the corresponding protons in the *anti*-facial isomer **34** of the same symmetry. The lower symmetry of the third isomer **33** sets it aside from the other two; significantly protons Ha and Hb are in accord with the earlier assignments (cf. boxed structures in Scheme 3). The value of this reaction is not only that it provides access to the desired O^5-[5]polynorbornane **32**, but that the co-formed O^3-[3]polynorbornane **34** has a cavity structure with potential O-binding sites at the cavity entrance, a structural feature of interest in its own right.

In a reaction designed to incorporate a terminal epoxide oxygen as part of the polarofacial array, we were able to capitalise on the fact that:

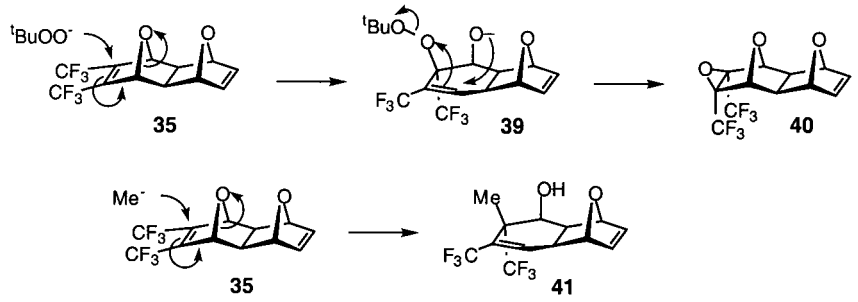
- 2,3-bis(trifluoromethyl)norborn-2-enes do not participate in Mitsudo coupling.[15]
- 2,3-bis(trifluoromethyl)-7-oxanorborn-2-enes will undergo epoxidation with nucleophilic reagents.
- norbornene epoxides do not thermally ring-open to 1,3-dipoles, so do not participate in the ACE reaction.

Treatment of bis-alkene **36**, prepared by Ru-catalysed addition of DMAD to **35**,[16] with excess *t*-butyl hydroperoxide/methyl lithium reagent at −78°C afforded the bis-epoxide **38** (43%) (Scheme 6) where attack has occurred at both the π-bonds.[17] The intermediate cyclobutene epoxide **37** (58%) could be isolated if one equivalent of epoxidising agent was employed, thereby demonstrating the site selectivity applying in this bis-alkene system.

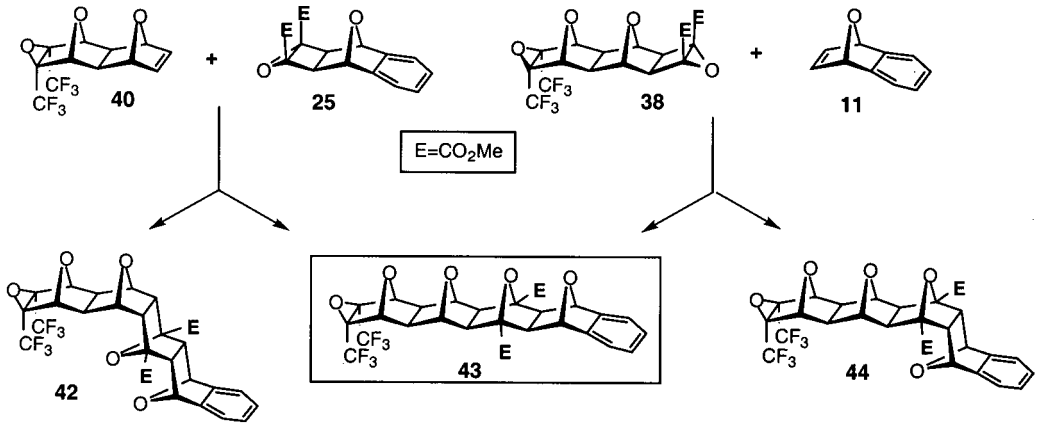
The fact that 7-oxanorbornenes **35** and **37** can be epoxidised at the trifluoromethyl-substituted π-bond are further examples of a general reaction proceeding with participation of the oxygen bridge.[19,20] For example, reaction of **35** is proposed to occur by initial S_N2' attack of $^tBuOO^-$ at the π-bond from the *exo*-face occurs with concomitant ring-opening of the oxa-bridge of form intermediate **39** (Scheme 7); ring reclosure of **39** via an SNi′ process yields epoxide **40** by displacement of $^tBuO^-$. This mechanism is supported by the isolation of by-product **41** derived from competitive attack of methyl carbanion on **35** to form a ring-opened intermediate which is unable to reclose thereby leading to **41**, and by the fact that the analogous carbon bridged bis(trifluoromethyl)norbornenes are not epoxidised under these reaction conditions.

A parity reversal approach[21] can be used to access the penta-oxabridged system **43**. In the first case, the cyclobutene epoxide **25** carried the benzene ring (acting as the nominal effector group) and was reacted with the dioxasesquinorbornene **40** bearing the norbornene epoxide grouping (acting as the alternative effector group) Thus, reaction of cyclobutene epoxide **25** with the π-bond of 7-oxanorbornene **40** produced the *syn*-facial adduct **43** (37%) which has five *syn*-related oxa-bridges, one of which is in an epoxide ring. The *anti*-facial isomer **42** (48%) with four oxygen on the upper face was also formed (Scheme 8).

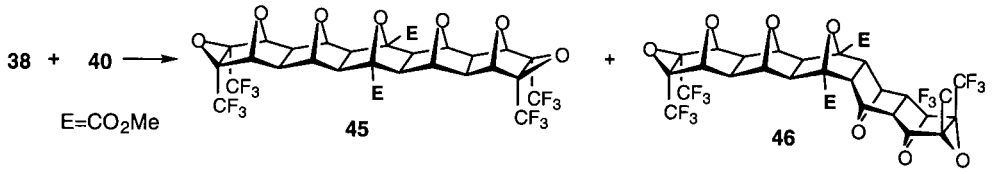
In the parity reversal process, the norbornene epoxide is contained in the cyclobutene epoxide reagent **38**, while the benzene ring is transported by the alkene reagent **11**. The penta-bridged isomer **43** was formed in 34% yield,



Scheme 7.



Scheme 8.



Scheme 9.

admixed with the *anti*-facial adduct **44** (44% yield). In both cases, the *syn*-facial isomer is dominated by the *anti*-facial product, but is still formed in workable yields.

We have been able to extend this process further by reaction of the epoxy-7-oxanorbornene **40** with the cyclobutene epoxide **38** to afford a [5]polynorbornane with seven *syn*-facial oxygens (Scheme 9). The *syn*-facial isomer **45** (C2v-symmetry, four overlapping singlet methine proton resonances) was produced in 31% yield accompanied by the less symmetrical sinusoidal-shaped isomer **46** (eight different singlet methine proton resonances) (40%) (Scheme 9). Compound **45** with seven *syn*-facial oxygens represents the most extended polarofacial system of its type yet produced.

The structure of the hepta-bridged system **45** has been optimised using AM1 calculations and this is shown in Fig. 2. The arc-shaped curvature of the polynorbornane backbone is typical,[22] while the epoxide end-groups significantly increase the curvature at the termini. The other feature to note is that the curvature maximises the exposure of the hydrophilic polar face, whereas the lipophilic undersuface is more protected.

2.2. 1,3,4-Oxadiazole coupling of 7-oxabenzonorbornene revisited

In our early endeavours to employ 1,3,4-oxadiazole coupling of norbornenes for the preparation of *syn*-facial polynorbornanes, 7-oxabenzonorbornadiene **11** was reacted with 2,5-bis(trifluoromethyl) 1,3,4-oxadiazole **47**.[23–26] We found that the *anti*-facial product **51** was the exclusive product with no evidence for the *syn*-facial isomer **50** (Scheme 10). In view of the formation of significant amounts of the *syn*-facial polynorbornane **27** as well as the *anti*-facial isomer **28** from ACE coupling of **25** with **26a** (Scheme 4), we were curious to find if the 1,3,4-oxadiazole protocol could be employed. We reasoned that similar 1,3-dipole intermediates were involved and the differences in stereoselectivity might simply relate to the substituent size (CF_3 v ester). Indeed, this approach was successful and replacement of a single trifluoromethyl substituent in 1,3,4-oxadiazole **47** by an ester group as in 1,3,4-oxadiazole **48** was sufficient to produce substantial quantities of the *syn*-facially-coupled product **52** (55% yield). This substituent effect was even more pronounced using the diester-substituted 1,3,4-oxadiazole **49** which now afforded the *syn*-facial adduct **27** as the major product (60% yield). Symmetry considerations were used to assign structures to the coupled products based on ^{1}H NMR data. Compounds **27** and **28** produced in the 1,3,4-oxadiazole coupling with **49** were identical to those formed using the ACE method (vide supra).

2.3. Aza-systems

The exclusive *exo*,*exo*-stereoselectivity exhibited in the ACE coupling of cyclobutene epoxides with 7-azabridged-benzonorbornadienes opened the way to produce *syn*-facial

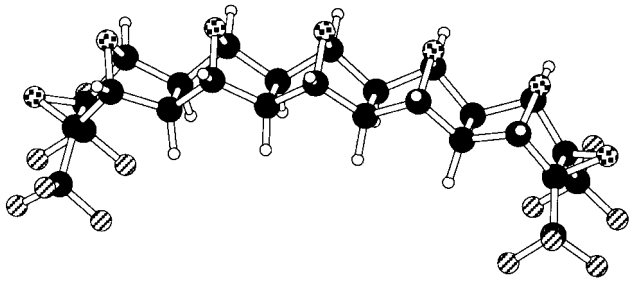
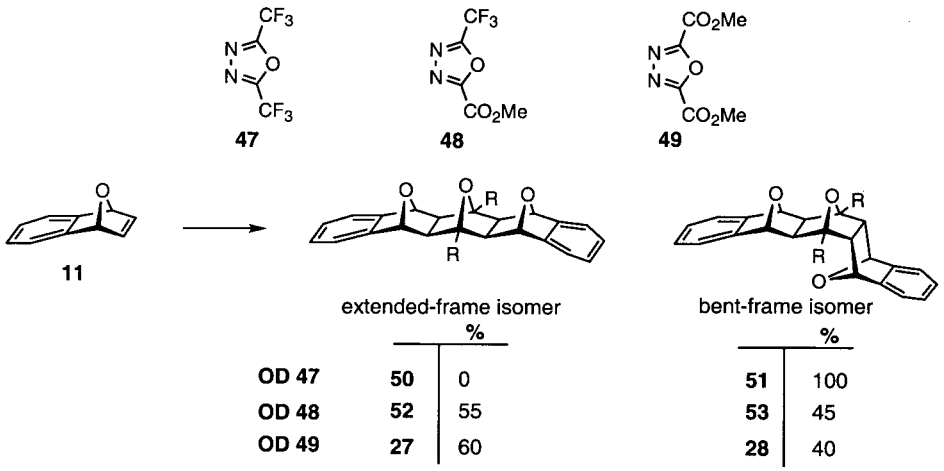


Figure 2. AM1 optimised structure for **45** (esters omitted).



Scheme 10.

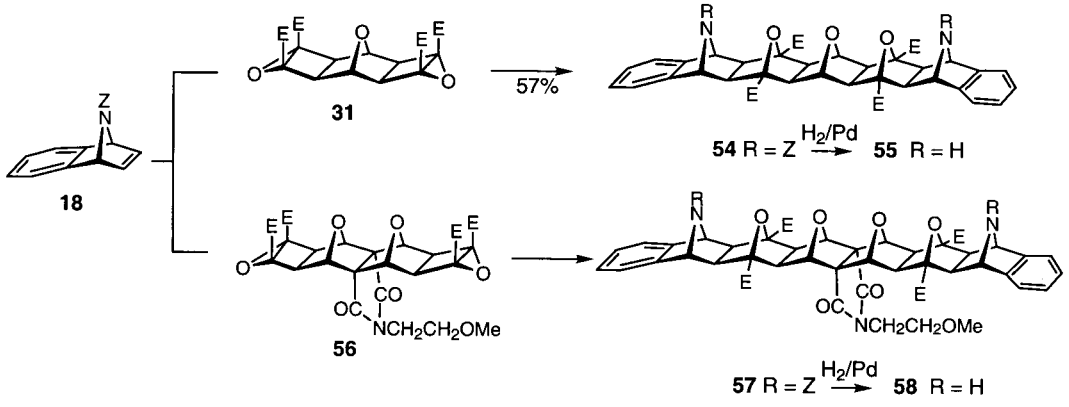
NO-bridged polynorbornanes free from isomer contamination. The examples studied to date are both directed at medium length polynorbornanes, but serve to demonstrate the general principles involved. 7-*Z* 7-aza-benzonorbornadiene **18** in which the *N*-bridge is protected with a *Z*-group was used in the first prototype reaction and heated directly with bis-epoxide **31** to produce the coupled NO^3N-[5]polynorbornane **54**. The second example also used the *N*–*Z* dipolarophile **18**. Thus, reaction of **18** with bis-epoxide **56** produced the NO^4N-[6]polynorbornane **57** (Scheme 11). The *Z*-protecting group was removed from **54** and **57** by hydrogenolysis (H_2, Pd/C) to produce the corresponding *NH*-compound **55** and **58** respectively. The ^{1}H NMR spectra of adduct **57**, possessing the *N*–*Z* substituent was unsymmetrical at room temperature, but became symmetrical on warming to 80°C; such behaviour is well precedented.[27] The related *NH* compounds were not subject to such temperature dependant change and standard ^{1}H NMR spectroscopy could be used to establish the C_{2v}-symmetry of adducts **55** and **58**.

This study has established the stereoselectivity of the reaction of heterobridged norbornanes with cyclobutene epoxides and shown how this extension of the ACE coupling reaction can be used to form hetero-bridged polynorbornanes. This methodology has opened the way to produce a new class of rigid alicyclic polarofacial molecules in which the polar face is provided by all *syn* oxygen or nitrogen bridges. The fact that dual alkene and dual cyclobutene epoxides can participate twice in this building protocol allows effective entry to [*n*]polynorbornanes containing significant numbers of fused 7-oxa (or 7-aza)norbornanes. Future plans include the development of reagents with aziridine rings replacing the epoxide rings thereby opening the opportunity to prepare all-nitrogen bridged N^n[*n*]polynorbornanes. Early endeavours in this aza-ACE coupling protocol are already in hand[28] and their application to multi hetero-bridged [*n*]polynorbornane synthesis will be the subject of future reports.

3. Experimental

Melting points, which are uncorrected, were obtained on a Reinhart Micro hot stage melting point apparatus Model YOSCO No 67885. ^{1}H NMR spectra were recorded at 300 or 400 MHz. ^{13}C NMR spectra were recorded by using an inverse gated sequence at 75.4 MHz. Unless otherwise stated all data were acquired using $CDCl_3$ solutions with TMS as an internal standard and are reported on the appropriate δ_H and δ_C scales. Coupling constants are reported in Hz.

The silica gel used for column chromatography was silica

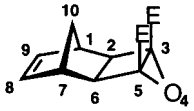


Scheme 11. E=CO_2Me, Z=CO_2CH_2Ph.

gel 60 (230–400 mesh). TLC was performed on Merck aluminium sheets coated with silica gel 60 F_{254}. Centrifugal radial chromatography was carried out with a Chromatotron, Model No 7924T, using 1 mm plates coated with silica gel 60 F_{254}.

Mass spectra were obtained by EI or PCI (photochemical ionisation) on a Hewlett Packard 5988A spectrometer or by EI or ESMS (electrospray mass spectrometry) on a Micromass Platform II single quadripole mass spectrometer.

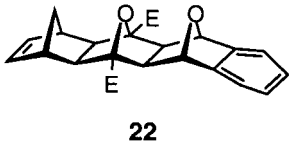
MeLi refers to a 1.6 M solution in diethyl ether and ^{t}BuOOH refers to a 3.8 M solution in toluene. Both solutions were standardised before use. All solvents were removed under reduced pressure.



21

3.1. Dimethyl (1α,2β,3α,5α,6β,7α)-4-oxatetracyclo-[5.2.1.0^{2,6}.0^{3,5}]deca-8-ene-3,5-dicarboxylate (21) (standard epoxidation procedure)

The diester **20** (0.85 mmol, 0.20 g) was dissolved in anhydrous THF and cooled, with stirring to −78°C under an atmosphere of nitrogen. A solution of ^{t}BuOOH in toluene (0.5 mL, 1.9 mmol) was added to the mixture and after a further 5 min a solution of MeLi in diethyl ether (0.54 mL, 0.85 mmol) was added. The solution was then allowed to stir for 3 h at room temperature, diluted with CH_2Cl_2 and washed with saturated aqueous sodium sulfite, water and dried over sodium sulfate. The dry organic phase was freed of solvent to afford the product **21** as a viscous oil (0.17 g, 79%) which solidified on cooling. Mp 95–97°C; δ_H 1.51 (1H, d, J=9.8 Hz, H10), 1.76 (1H, d, J=9.8 Hz, H10), 2.27 (2H, s, H2,6), 3.22 (2H, bs, H1,7), 3.79 (6H, s, CO_2CH_3), 6.15 (2H, bs, H8,9). δ_C 41.65, 41.73, 48.89, 52.68, 66.67, 137.49, 164.74. HRMS $C_{13}H_{14}O_5$ requires m/z 250.0841, found 250.0868.



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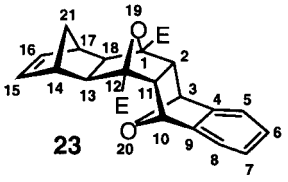
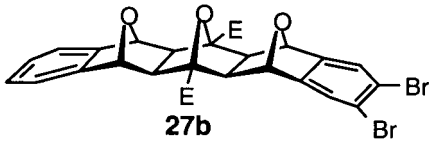


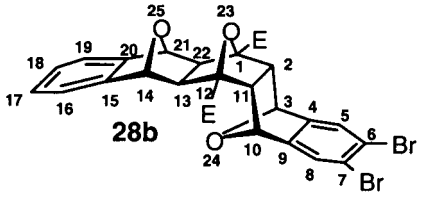
23

3.2. Dimethyl (1α,2β,3α,10α,11β,12α,13β,14α,17α,18β) 19,20-dioxaheptacyclo [10.6.1.1^{3,10}.1^{14,17}.1^{4,9}.0^{2,11}.0^{4,9}.0^{13,18}] henicosa-4,6,8,15-tetraene-1,12 dicarboxylate (22) and dimethyl (1α,2α,3β,10β,11α,12α,13β,14α,17α,18β) 19,20-dioxaheptacyclo[10.6.1.1^{3,10}.1^{14,17}.1^{4,9}.0^{2,11}.0^{4,9}.0^{13,18}] henicosa-4,6,8,15-tetraene-1,12 dicarboxylate (23) (standard coupling procedure)

The epoxide **21** (84 mg, 0.34 mmol) and the alkene **11** (58 mg, 0.40 mmol) were dissolved in CH_2Cl_2 (1 mL) and the solution heated in a sealed tube for 6 h at 140°. The solvent was removed and the residue, shown by ^{1}H NMR, to be a 7:5 mixture of isomer **22** and **23**. These products were separated by column chromatography (silica/CH_2CH_2–$CHCl_3$ gradient) to afford firstly isomer **23** (85 mg, 64%) followed by isomer **22** (26 mg, 20%) as heavy oils. **22**. δ_H 1.45 (1H, d, J=14 Hz, H21), 2.06 (2H, s, H 13,18), 2.39 (2H, s, H2,11), 2.57 (1H, d, J=14 Hz, H21), 2.68 (2H, s, H14,17), 3.95 (6H, s, CO_2CH_3), 5.22 (2H, s, H3,10), 6.12 (2H, bs, H15,16), 7.12 (2H, m, ArH), 7.23 (2H, m, ArH). δ_C 42.17, 43.98, 52.45, 55.05, 54.60, 80.36, 87.83, 119.36, 226.90, 139.37, 145.48, 169.88. LRMS m/z (PCI) M^+: 394. HRMS $C_{23}H_{23}O_6$ requires m/z 394.1416, found 394.1410 **23**. δ_H 1.57 (1H, d, J=9 Hz, H21), 2.49 (2H, s, H13,18), 2.53 (1H, d, J=9 Hz, H21), 2.61 (2H, s, H2,11), 2.65 (2H, s, H14,17), 3.87 (6H, s, CO_2CH_3), 5.31 (2H, s, H3,10), 6.20 (2H, bs, H15,16) 7.12 (2H, m, ArH), 7.24 (2H, m, ArH). δ_C 43.65, 44.12, 49.57, 52.35, 56.89, 77.98, 8.7, 3.3, 119.60, 126.80, 139.17, 146.23, 170.30. LRMS m/z (PCI) M^+: 394. HRMS $C_{23}H_{23}O_6$ requires m/z 394.1416, found 394.1421.



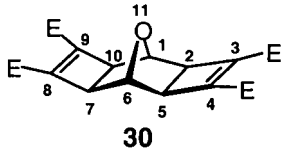
27b



28b

3.3. Dimethyl (1α,2α,3β,10β,11α,12α,13β,14α,21α,22β) 6,7-dibromo-23,24,25-trioxacoctacyclo[10.10.1.1^{3,10}.1^{14,21}.0^{2,11}.0^{4,9}.0^{13,22}.0^{15,20}]pentacosa-4,6,8,15,17,19-hexaene-1,12-dicarboxylate (27b) and dimethyl-(1α,2α,3β,10β,11α,12α,13β,14α,21α,22β) 6,7-dibromo-23,24,25-trioxacoctacyclo [10.10.1.1^{3,10}.1^{14,21}.0^{2,11}.0^{4,9}.0^{13,22}.0^{15,20}]pentacosa-4,6,8,15,17,19 hexaene-1,12-dicarboxylate (28b)

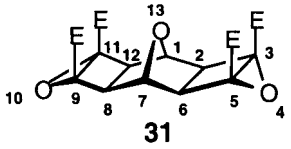
These isomers were prepared from the epoxide **25** (300 mg, 0.99 mmol) and alkene **26b** (300 mg, 0.99 mmol), separated by radial centrifugal chromatography, (EtOAc/hexane 2:1) and recrystallised from EtOAc/hexane. **27b**. (274 mg, 46%), mp 302–303°C; δ_H 2.69, 2.70 (4H, 2s, H2,11,13,22), 3.96 (6H, s, CO_2CH_3), 5.23, 5.24 (4H, 2s, H3,10,14,21) 7.16–7.18 (2H, m, ArH), 7.24–7.25 (2H, m, ArH), 7.51 (2H, s, H5,8); δ_C 50.37, 52,87, 56.02, 77.35, 80.18, 87.29, 119.41, 122.92, 125.09, 127.02, 145.30, 146.58, 169.94. m/z (ES) $(M+Na)^+$: 627, $(M+K)^+$: 643. HRMS $C_{26}H_{20}O_7Br_2$: calculated 601.9576; observed 601.9572. **28b**. (288 mg, 48%), mp 330–331°C; δ_H 2.31, 2.32 (4H, 2s H2,11,13,22), 4.03 (6H, s, CO_2CH_3), 5.23, 5.25 (4H, 2d, H3,10,14,21); 7.12–7.15 (2H, m, ArH), 7.21–7.26 (2H, m, ArH), 7.49 (2H, s, H5,8). δ_C 52.93, 54.33, 54.82, 79.64, 80.04, 87.74, 119.35, 122.99, 124.73, 127.07, 145.09, 146.14, 169.51. m/z (ES) $(M+Na)^+$: 627 $(M+K)^+$: 643; HRMS $C_{26}H_{20}O_7^{79}Br_2$: calculated 601.9576; observed 601.9578.



30

3.4. Tetramethyl (1α,2β,5β,6α,7β,10β) 11-oxatetracyclo[4.4.1.$0^{2,5}$.$0^{7,10}$.]undeca-3,8-diene-3,4,8,9-tetracarboxylate (30)

A mixture of adduct **29**[8] (2.0 g, 8.5 mmol), dimethyl acetylene dicarboxylate (3 g, 21 mmol) and RuH_2-(CO)(PPh_3)$_3$ (70 mg, catalytic) was heated neat at 80°C for 24 h, in a stirred, tightly stoppered flask. The resulting dark brown solution was cooled to room temperature and applied to a column of silica gel. The column was then eluted with a mixture of dichloromethane/petroleum spirit (1:1) until all the dimethyl acetylene dicarboxylate had been removed. The product was eluted from the column starting with a solvent mixture of ethyl acetate/petroleum spirit (1:5), gradually increasing polarity to pure EtOAc. The recovered solid was recrystallised from methanol to afford adduct **30** as colourless crystals (2.0 g, 61%), mp 196–198°C; ($C_{18}H_{18}O_9$ requires C, 57.14; H, 4.80. found: C, 56.82; H, 4.66%.). δ_H 2.97 (4H, s, H2,5,7,10), 3.79 (12H, s, CO_2CH_3), 4.38 (2H, s, H1,6). δ_C 46.55, 51.87, 69.49, 141.18,160.62. *m/z* (EI)M^+: 378; HRMS $C_{18}H_{18}O_9$: calculated 378.0951; observed 378.0948.



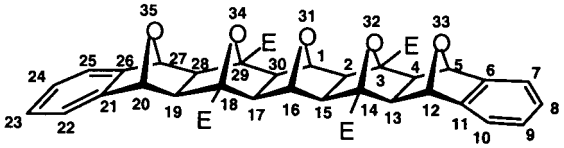
31

3.5. Tetramethyl (1α,2β,3α,5α,6β,7α,8β,9α,11α,12β) 4,10,13-trioxahexacyclo-[5.5.1.$0^{2,6}$.$0^{3,5}$.$0^{8,12}$.$0^{9,11}$]trideca-3,5,9,11-tetracarboxylate (31)

In a two-necked flask, fitted with septum, under a nitrogen atmosphere, was placed bis-cyclobutene diester **30** (1.0 g, 2.6 mmol) dissolved in dry THF (12 mL). The solution was then cooled to −78°C. Anhydrous ^{t}BuOOH (1.74 mL, 6.6 mmol), was added using a syringe. After 5–10 min, syringe addition of MeLi (2.37 mL, 3.6 mmol) was effected and a colour change occurred. After stirring for a further 15–20 min at −78°C, the solution was allowed to warm to room temperature and stirred for an additional 3 h. During that period the solution became less yellow in colour. Dichloromethane (30 mL) was then added to the flask, the contents transferred to a separating funnel and the organic phase washed with 10% aqueous sodium sulphite, water and dried ($MgSO_4$). Removal of solvent under vacuum yielded the crude bis-epoxide, which was recrystallised from a solution of CH_2Cl_2 and petroleum ether to yield the product **31** as colourless crystals (0.51 g, 48%), mp 314°C (dec). δ_H 2.60 (4H, s, H2,6,8,12), 3.83 (12H, s, CO_2CH_3), 5.68 (2H, s, H1,7). δ_C 50.16, 52.93, 63.46, 75.50, 163.83. *m/z* (EI) M^+: 410. HRMS $C_{18}H_{18}O_{11}$: calculated 410.0849; observed 410.0893.

3.6. Reaction of bis epoxide 31 with 7-oxabenzonorbornadiene 11

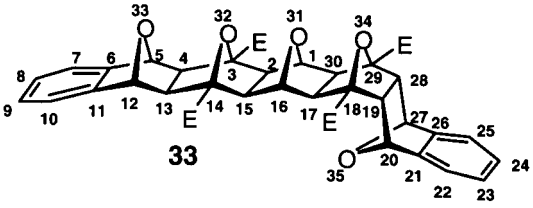
A solution of bis-epoxide **31** (16 mg, 0.04 mmol) and excess 7-oxabenzonorbornadiene **11** (33 mg, 0.23 mmol) in dichloromethane (2.5 mL) was heated in a sealed tube at 140°C for 3 h. The solvent was then evaporated under reduced pressure and the residue separated by centrifugal radial chromatography. The excess 7-oxabenzonorbornadiene was eluted using a solvent mixture of EtOAc/petroleum spirit (1:4). A solvent mixture containing methanol in EtOAc (1:99) was required to elute adducts **34** and **33** in that order. The solvent polarity was gradually increased to methanol/EtOAc (1:9) in order to elute adduct **32**. The solids recovered from chromatography were washed with methanol to afford the three isomers as colourless crystals The individual yields were calculated based on ^{1}H NMR analysis of the crude reaction mixture.



32

3.7. Tetramethyl (1α,2β,3α,4β,5α,12α,13β,14α,15β, 16α,17β,18α,19β, 20α,27α,28β,29α,30β) 31,32,33,34, 35-pentaoxadodecacyclo[14.14.1.$1^{3,14}$.$1^{5,12}$.$1^{18,29}$.$1^{20,27}$. $0^{2,15}$.$0^{4,13}$.$0^{6,11}$.$0^{17,30}$.$0^{19,28}$.$0^{21,26}$]pentatriaconta-6,8,10, 21,23, 25-hexaene-3,14,18,29-tetracarboxylate (32)

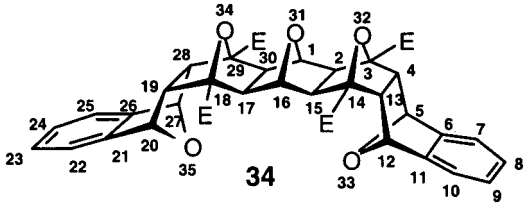
Yield 13%, mp 299°C (dec.); δ_H 2.16 (4H, s, H2,15,17,30), 2.28 (4H, s, H4,13,19,28), 3.94 (12H, s, CO_2CH_3), 4.32 (2H, s, H1,16), 5.19 (4H, s, H5,12,20,27); 7.12 (4H, m, H8,9,23,24), 7.20 (4H, m, H7,10,22,25). δ_C 52.62, 54.54, 55.18, 78.72, 80.11, 88.33, 119.39, 127.11, 145.21, 169.45. *m/z* (EI)M^+: 698, HRMS $C_{38}H_{34}O_{13}$: calculated 698.1999; observed 698.1997.



33

3.8. Tetramethyl (1α,2β,3α,4β,5α,12α,13β,14α,15β, 16α,17β,18α,19α,20β,27β,28α,29α,30β) 31,32,33,34,35-pentaoxadodecacyclo[14.14.1.$1^{3,14}$.$1^{5,12}$.$1^{18,29}$.$1^{20,27}$.$0^{2,15}$. $0^{4,13}$.$0^{6,11}$. $0^{17,30}$.$0^{19,28}0^{21,26}$]pentatriaconta-6,8,10,21,23, 25-hexane-3,14,18,29-tetracarboxylate (33)

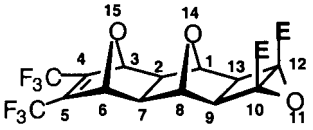
Yield 40%, mp 312°C (dec.); δ_H 2.34 (2H, s, H4,13), 2.37 (2H, s, H2,5), 2.59 (2H, s, H19,28), 2.63 (2H, s, H17,30), 3.85 (6H, s, CO_2CH_3), 3.94 (6H, s, CO_2CH_3), 4.28, (2H, s, H1,16), 5.21 (2H, s, H5,12), 5.26 (2H, s, H20,27), 7.12 (4H, m, H8,9,23,24), 7.22 (4H, m, H7,10,22,25); δ_C 51.29, 52.49, 52.53, 54.47, 55.36, 57.15, 77.90, 78.88, 80.15, 87.79, 88.40, 119.34, 119.68, 127.05, 127.08, 145.18, 145.57, 169.55, 169.74; *m/z* (EI)M^+: 698; HRMS $C_{38}H_{34}O_{13}$: calculated 698.1999; observed 698.2007.



34

3.8. Tetramethyl (1α,2β,3α,4α,5β,12β,13α,14α,15β, 16α,17β,18α,19α,20β,27β,28α,29α,30β) 31,32,33,34, 35-pentaoxadodecacyclo[14.14.1.1^{3,14}.1^{5,12}.1^{18,29}.1^{20,27}. 0^{2,15}.0^{4,13}.0^{6,11}.0^{17,30}.0^{19,28}.0^{21,26}]pentatriacont-6,8,10,21, 23,25-3,14,18,29-tetracarboxylate (34)

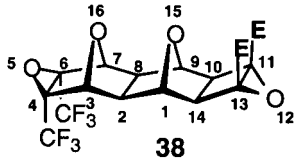
Yield 17%; mp 318°C; δ_H 2.59 (4H, s, H4,13,19,28), 2.82 (4H, s, H2,15,17,30), 3.85 (12H, s, CO_2CH_3), 4.24 (2H, s, H1,16), 5.33 (4H, s, H5,12,20,27), 7.12 (4H, m, H8,9,23,24), 7.20 (4H, m, H7,10,22,25). δ_C (DMSO) 50.72, 52.28, 56.76, 77.05, 79.50, 87.16, 119.75, 126.64, 146.10, 169.30; δ_C ($CDCl_3$) 51.34, 52.43, 57.23, 77.84, 79.16, 87.94, 119.67, 126.99, 145.75, 169.89. HRMS calculated for $C_{38}H_{34}O_{13}$ *m/z* 698.1999; observed 698.2017.



37

3.9. Dimethyl (1α,2β,3α,6α,7β,8α,9β,10α,12α,13β) 4,5-bis(trifluoromethyl)-11,14,15-trioxahexacyclo [6.5.1.1^{3,6}.0^{2,7}.0^{9,13}.0^{10,12}]pentadeca-4-ene-10,12-dicarboxylate (37)

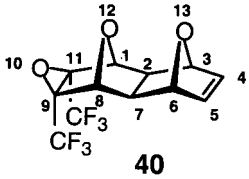
This compound was prepared from the alkene **36** (69.6 mg, 0.20 mmol), ^{t}BuOOH (0.08 mL, 0.3 mmol) and MeLi (0.08 mL, 0.14 mmol) using a method identical to that described for compound **38**. The product was obtained as a white powder (42 mg, 58% yield) which was sparingly soluble in CH_2Cl_2, $CHCl_3$ and acetone, mp 242–243°C; δ_H 2.1 (2H, s, H2,7), 2.7 (2H, s, H9,13), 3.8 (6H, s, CO_2CH_3), 5.2 (2H, s, H1,8), 5.3 (2H, s, H3,6); δ_C 47.74, 51.26, 52.94, 63.32, 77.88, 82.1, 120 (q, J_{C-F}=270 Hz), 141 (q, J_{C-F}=46.0 Hz), 163.87; *m/z* (PCI) $(M+H)^+$: 457.



38

3.9. Dimethyl (1α,2β,3α,4β,6β,7α,8β,9α,10β,11α,13α, 14β) 4,6-bis(trifluoromethyl)-5,12,15,16-tetraoxaheptacyclo[7.5.1.1^{3,7}.0^{2,8}.0^{4,6}.0^{10,14}.0^{11,13}]hexadeca-11,13-dicarboxylate (38)

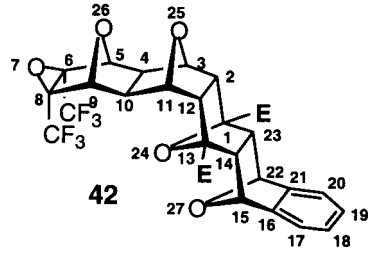
The alkene **36**[16] (241 mg, 0.55 mmol) and ^{t}BuOOH (0.43 mL, 1.64 mmol) were added to dry THF (10 mL) and the reaction mixture was stirred under a nitrogen atmosphere at −78°C for 10 min after which methyl lithium (0.75 mL, 1.2 mmol) was added. After a further 15 min the cooling bath was removed, the solution allowed to warm to room temperature and stirring maintained for a further 2 h. The resulting crude reaction mixture was transferred, using CH_2Cl_2, to separating funnel, the organic phase washed with saturated aqueous sodium sulphite, water, and dried. The solvent was removed to afford a white powder which was recrystallised (EtOAc/hexane) to afford the product as colourless needles (111 mg, 43%), mp: 197–198°C; δ_H 2.4 (2H, s, H2,8), 2.6 (2H, s, H10,14), 3.8 (6H, s, CO_2CH_3), 4.7 (2H, s, H3,7), 5.2 (2H, s, H1,9); δ_C 47.70, 50.42, 52.69, 62.2, (q, J_{C-F}=41.3 Hz), 62.74, 77.0, 77.61, 124.9 (q, J_{C-F}=277 Hz), 163.58. *m/z* (PCI) M^+: 472.



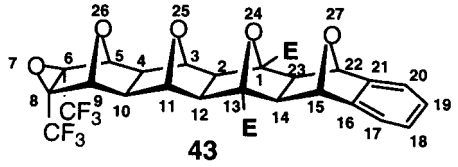
40

3.10. (1α,2β,3α,6α,7β,8α,9β,11β) 9,11-Bis(trifluoromethyl)-10,12,13-trioxapentacyclo [6.3.1.1^{3,6}.0^{2,7}.0^{9,11}]-trideca-4-ene (40)

This compound was prepared from the alkene **35**[16] (100 mg, 0.34 mmol), ^{t}BuOOH (0.11 mL, 0.42 mmol) and MeLi (0.18 mL, 0.3 mmol) using the method described for compound **38**. The residue from the reaction was separated by centrifugal radial chromatography (hexane/EtOAc gradient) to afford initially the epoxide **40** (68 mg, 65%), mp 125–126°C; δ_H 2.42 (2H, s, H2,7) 4.65 (2H, s, H1,8), 4.98 (2H, s, H3,6), 6.45 (2H, s, H4,5); δ_C 46.76, 64 (q, J_{C-F}=42 Hz), 76.11, 79.99, 122 (q, J_{C-F}=276.3 Hz), 137.63; *m/z* (APCI) $(M+H)^+$: 314.9. HRMS $C_{12}H_8O_3F_6$ requires *m/z* 314.0378, found 314.0378. Continued elution afforded (1α,2β,3α,4α,8α) 4-methyl-4,5-bis(trifluoromethyl)-11-oxatricyclo[6.2.1.0^{2,7}]undeca-5,9-dien-3-ol (**41**) (6.4 mg, 6%), mp 69–70°C; δ_H 1.58 (3H, s, CH_3), 2.36 (2H, s, H2,7); 3.26 (1H; d *J* 9.03 Hz, OH); 4.20–4.24 (1H, m, H3), 4.80 (1H, s H1 or H8), 5.11 (1H, s, H8 or H1), 6.40–6.43, 6.58–6.61 (2H, 2m, H9,10), 6.94 (1H, s, H6); δ_C 15.36, 38.07, 39.46, 49.11 (m), 70.11, 80.14, 87.57, 123.01 (q J_{C-F}=273 Hz), 126.14 (q, J_{C-F}=273 Hz), 128.70 (m), 134.00, 139.53, 139.62; *m/z* (EI) $(M+H)^+$: 314.9.



42



43

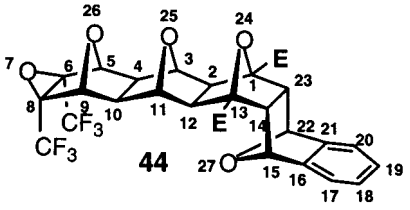
3.11. (1α,2β,3β,4α,5β,6α,8α,9β,10α,11β,12β,13α,14β, 15α,22α, 23β) Dimethyl 6,8-bis(trifluoromethyl)-7,24, 25,26,27-pentaoxadecacyclo[11.10.1.1^{3,11}.1^{5,9}.1^{15,22}. 0^{2,12}.0^{4,10}. 0^{6,8}.0$^{14.23}$.0$^{16.21}$]heptacosa-16,18,20-triene-1,13-dicarboxylate (42) and (1α,2β,3α,4β,5α,6β,8β,9α,10β, 11α,12β,13α,14β,15α,22α,23β) dimethyl 6,8-bis(trifluoromethyl)-7,24,25,26,27-pentaoxadecacyclo-[11.10.1.1^{3,11}.1^{5,9}.1^{15,22}. 0^{2,12}.0^{14,10}. 0^{6,8}.0$^{4.23}$. 0$^{16.21}$] heptacosa-16,18, 20-triene-1,13-dicarboxylate (43)

These isomers were prepared from the epoxide **25** (144 mg,

0.48 mmol) and the alkene **40** (150 mg, 0.48 mmol) using the standard coupling procedure and the resultant products separated by centrifugal radial chromatography (EtOAc/hexane) and recrystallised to afford isomer **43** (109 mg, 37%) and **42** (142 mg, 48%).

42. Mp 233–235°C; δ_H 2.35 (2H, s), 2.49 (2H, s), 2,55 (2H, s), 3.94 (6H, s, CO_2CH_3), 4.57 (2H, s), 4.64 (2H, s), 5.15 (2H, s, H14,23), 7.11–7.12 (2H, m, ArH), 7.17–7.18 (2H, m, ArH); δ_C 49.00, 50.25, 52.87, 56.98, 62.11 (q, J_{C-F}=48 Hz), 76.85, 77.18, 80.07, 87.77, 119.29, 121.35 (q, J_{C-F}=276 Hz), 127.05, 145.06, 169.93; *m/z* (ES) $(M+Na)^+$: 639, $(M+K)^+$: 655; HRMS $C_{28}H_{22}O_9F_6$: calculated 616.1168; observed 616.1174.

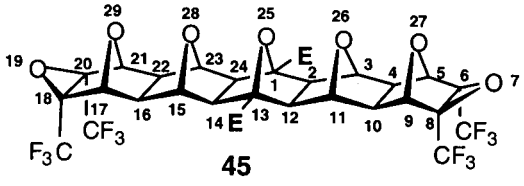
43. Mp: 332–333°C; δ_H 2.3 (6H, s, H2,4,10,12,14,23), 3.9 (6H, s, CH_3), 4.5 (2H, s, H3,11), 4.6 (2H, s, H5,9), 5.2 (2H, s, H15,22), 7.16–7.2 (4H, m, H17,18,19,20); δ_C 48, 53, 54, 55, 62 (q, J_{C-F}=47 Hz), 77, 79, 80, 88, 114, 119, 122 (q, J_{C-F}=270 Hz), 127, 169; *m/z* (ES) $(M+Na)^+$: 634; HRMS $C_{28}H_{22}O_9F_6$: calculated 616.1168; observed 616.1176.

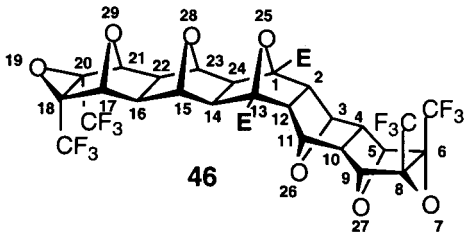


3.12. (1α,2β,3α,4β,5α,6β,8β,9α,10β,11α,12β,13α,14β, 15α,22βα,23β) Dimethyl 6,8-bis(trifluoromethyl)-7,24, 25,26,27-pentaoxodecacyclo[11.10.1.1^{3,11}.1^{5,9}.1^{15,22}.0^{2,9}. 0^{4,10}.0^{6,8}.0$^{4.23}$.0$^{16.21}$] heptacosa-16,18,20-triene-1,13-dicarboxylate (43) and (1α,2β,3α,4β,5β,6β,8β,9α, 10β,11α,12β,13α,14α,15β,22β,23α) dimethyl 6,8-bis(trifluoromethyl)-7,24,25,26,27-pentaoxodecacyclo-[11.10.1.1^{3,11}. 1^{5,9}.1^{15,22}.0^{2,9}.0^{4,10}.0^{6,8}.0$^{4.23}$.0$^{16.21}$]heptacosa-16,18,20-tri-ene-1,13-dicarboxylate (44)

The bis-epoxide **38** (92 mg, 0.19 mmol) and the alkene **11** (29 mg, 0.2 mmol) were added to CH_2Cl_2 (0.5 mL) and the reaction mixture was heated in a sealed tube at 140°C for 5 h. The residue obtained by removing the solvent was purified by centrifugal radial chromatography to afford the turn isomer **44** (44%) and the extended isomer **43** (34%). Both products were recrystallised from EtOAc and hexane.

44. Mp: 301–302°C; δ_H 2.51 (2H, s, H4,10) 2.62 (2H, s, H14,23), 2.77 (2H, s, H2,12) 3.89 (6H, s, CH_3), 4.45 (2H, s, H3,11), 4.63 (2H, s, H5,9), 5.34 (2H, s, H15,22), 7.14–7.28 (4H, m, H17,18,19,20). δ_C 48.84, 51.43, 52.86, 57.32, 62 (q, J_{C-F}=42.6 Hz), 77.26, 77.92, 79.72, 87.79, 119.76, 122 (q, J_{C-F}=265 Hz), 127.18, 145.43, 169.93; *m/z* (ES) $(M+Na)^+$: 634.2; HRMS $C_{28}H_{22}O_9F_6$: calculated 616.1168; observed 616.1172.



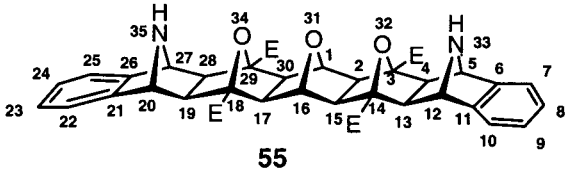


3.13. Dimethyl (1α,2β,3α,4β,5α,6α,8α,9α,10β,11α, 12β,13α,14β,15α,16β,17α,18α,20α,21α,22β,23α,24β) 6,8,18,20-tetrakis(trifluoromethyl)-7,19,25,26,27,28,29-heptoxadodecacyclo [11.11.1.1^{3,11}.1^{5,9}.1^{15,23}.1^{17,21}.0^{2,12}. 0^{4,10}.0^{6,8}.0^{14,24}.0^{16,22}.0^{18,20}]octacosa-1,13-dicarboxylate (45) and dimethyl (1α,2β,3α,4β,5α,6α,8α,9α,10β, 11α,12β,13α,14α,15β,16α,17β,20β,21β,22α,23β,24α) 6,8,18,20 tetrakis (trifluoromethyl)-7,19,25,26,27,28,29-heptoxadodecacyclo [11.11.1.1^{3,11}.1^{5,9}.1^{15,23}.1^{17,21}.0^{2,12}. 0^{4,10}.0^{6,8}.0^{14,24}.0^{16,22}.0^{18,20}]octacosa-1,13-dicarboxylate (46)

The products were prepared from the alkene **40** (32 mg, 0.10 mmol) and the bis-epoxide **38** (48 mg, 0.10 mmol) by the standard thermal method, separated by centrifugal radial chromatography (EtOAc/hexane 1:1) and recrystallised from EtOAc/hexane.

45. Mp: 334–335°C; δ_H 2.34 (8H, s, H2,4,10,12,14,16, 22,24), 3.94 (6H, s, CO_2CH_3), 4.45, 4.61 (8H, 2s, H3,5,9,11,15,17,21,25); *m/z* (ES) $(M+Na)^+$: 809, $(M+K)^+$: 825; HRMS $C_{30}H_{22}O_{11}F_{12}$: calculated 786.0971; observed 786.0973.

46. Mp: >350°C; δ_H 2.39, 2.40 (4H, 2s, H2,12,14,24), 2.50, 2.53 (4H, 2s, H4,10,11,22), 3.91 (6H, s, CO_2CH_3) 4.38 (2H, s), 4.59 (2H, s), 4.67 (2H, s) 4.74 (2H, s); δ_C 48.78, 49.03, 50.67, 51.33, 53.01, 57.01, 77.06, 77.11, 77.28, 77.87, 79.44, 88.15, 169.56; *m/z* (ES) $(M+Na)^+$: 809, $(M+K)^+$: 825; HRMS $C_{30}H_{22}O_{11}F_{12}$: calculated 786.0971; observed 786.0958.



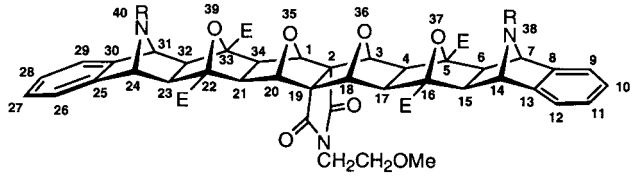
3.14. Tetramethyl (1α,2β,3α,4β,5α,12α,13β,14α,15β, 16α,17β,18α,19β,20α,27α,28β,29α,30β) 33,35-diaza-31,32,34-trioxa-dodecacyclo[14.14.1.1^{3,14}.1^{5,12}.1^{18,29}.1^{20,27}. 0^{2,15}.0^{4,13}.0^{6,11}.0^{17,30}.0^{19,28}.0^{21,26}] pentatriaconta-6,8,10,21, 23,25-hexaene-3,14,18,29-tetracarboxylate (55)

A solution of bis-epoxide **31** (100 mg, 0.245 mmol) and 7-azabenzonorbornadiene **18** (160 mg, 0.578 mmol) in benzene (2 mL) containing three drops of triethylamine was heated at 140°C for 2 h in a stainless steel bomb. Solvent was then evaporated in vacuo and residue subjected to radial chromatography (petroleum ether/EtOAc 5:1, then the solvent polarity was gradually increased to MeOH/EtOAc

(1:99) to afford compound **54** as a colourless solid (134 mg, 57%).

A solution of the bis-(benzyloxycarbonyl) derivative **54** (42 mg, 0.044 mmol) in ethanol (60 mL) and 10% Pd/C (30 mg) was shaken in a Parr hydrogenator overnight at 30 psi. The catalyst was removed by filtration and solvent evaporated off in vacuo to afford a solid product that was purified by radial chromatography (MeOH, EtOAc) (1:5) to produce the title compound **55** (11 mg, 36%).

55. Mp: 172–175°C; δ_H 2.17 (4H, s, H2, 15, 17, 30), 2.22 (4H, s, H4, 13, 19, 28), 3.96 (12H, s, CO_2Me), 4.34 (2H, s, 1, 16), 4.36 (4H, s, H5, 12, 20, 27), 7.09 (4H, m, H8, 9, 23, 24), 7.16 (4H, m, H7, 10, 22, 25); δ_c 52.72, 54.78, 54.98, 63.31, 79.04, 89.24, 119.86, 126.64, 145.34, 168.96; *m/z* HRMS $C_{38}H_{36}O_{11}N_2$: Calcd 697.2397 $(M+H)^+$; observed 697.2418 (M+H).



57 R=$COOCH_2Ph$

58 R=H

3.15. (1α,2β,3α,4β,5α,6β,7α,14α,15β,16α,17β,18α,19β,20α,21β,22α,23β,24α,31α,32β,33α,34β) N-(β-methoxyethyl) 38,40-di(benzyloxycarbonyl)-5,6,23,33-tetra(methoxycarbonyl)-37,40-diaza-35,36,37,39-tetraoxatetradecacyclo[18.14.1.1^{3,18}.1^{5,17}.1^{7,14}.1^{22,33}.1^{24,31}.0^{2,19}.0^{4,17}.0^{6,15}.0^{8,13}.0^{21,34}.0^{23,32}.0^{25,30}]tetraconta-8,10,12,25,27,29-hexaene-2,19-dicarboximide (57)

A solution of bis-epoxide **56** (50 mg, 0.083 mol) and *N*-(carbobenzyloxy)-7-azabenzonorbornadiene **18** (55 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was heated at 140°C for 2 h in a stainless steel bomb. Solvent was evaporated off in vacuo and the solid residue subjected to radial chromatography (petroleum ether/EtOAc 5:1, then the solvent polarity was gradually increased to pure EtOAc) to afford a pure adduct **57** as a colourless solid (48 mg, 50%, mp>340°C).

^{1}H NMR ($CDCl_3$, at 80°C) δ 2.16 (4H, s); 2.45 (4H, s); 2.73 (3H, s); 3.41–3.49 (4H, m); 3.88 (12H, s); 4.65 (4H, s); 4.99 (2H, m); 5.04 (4H, s); 5.19 (2H, d, *J*=6.3 Hz); 7.07–7.29 (18H, m). *m/z* HRMS $C_{63}H_{57}O_{19}N_3$ calculated 1159.3586 (M^+); observed: 1159.3590.

3.16. (1α,2β,3α,4β,5α,6β,7α,14α,15β,16α,17β,18α,19β,20α,21β,22α,23β,24α,31α,32β,33α,34β) N-(β-methoxyethyl) 5,6,23,33-tetra(methoxycarbonyl)-37,40-diaza-35,36,37,39-tetraoxa-tetradecacyclo [18.14.1.1^{3,18}.1^{5,17}.1^{7,14}.1^{22,33}.1^{24,31}.0^{2,19}.0^{4,17}.0^{6,15}.0^{8,13}.0^{21,34}.0^{23,32}.0^{25,30}]tetraconta-8,10,12,25,27,29-hexaene-2,19-dicarboximide (58)

A solution of the bis-(benzyloxycarbonyl) derivative **57** (30 mg, 0.026 mmol) in ethanol (100 mL) and 10% Pd/C (50 mg) was shaken in a Parr hydrogenator overnight at 30 psi. The catalyst was removed by filtration and solvent evaporated off in vacuo to afford a solid product which was purified by radial chromatography (petrol ether/EtOAc 1:1, then the solvent polarity was gradually increased to EtOAc, 10% methanol) to afford the title product **58** (15 mg, 38%).

Mp 310°C, dec. δ_H 2.15 (4H, s); 2.35 (4H, s); 2.69 (3H, s); 3.43 (2H, t, *J*=4.5 Hz); 3.51 (2H, t, *J*=4.3 Hz); 3.98 (12H, s); 4.36 (4H, s); 4.71 (4H, s); 7.05–7.08 (4H, m); 7.11–7.16 (4H, s); δ_C 30.08; 53.15; 53.34; 55.51; 63.66; 71.24; 82.66; 89.60; 120.16; 127.08; 145.61; 168.67; 173.06; *m/z* HRMS $C_{47}H_{46}O_{15}N_3$: calculated 892.2929 $(M+H)^+$; observed: 892.2916 (M+H).

Acknowledgements

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conducted at room temperature using 10 mol% of *tert*-BuO^-.[18]

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