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The Regiochemistry of Carbenoid Insertion into Zirconacycles

George J. Gordon, Tim Luker, Mark W. Tuckett and Richard J. Whitby*

Department of Chemistry, University of Southampton, Highfield, Southampton, Hampshire SO17 1BJ, UK

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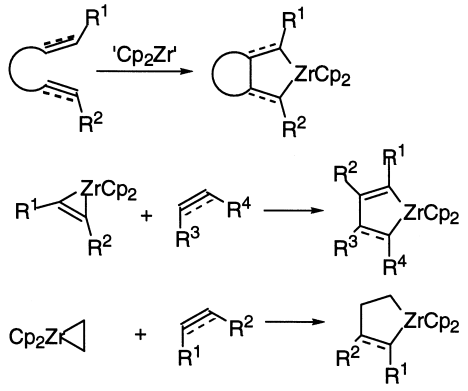
Abstract—The regioselectivity of insertion of lithium chloroallylides (allyl carbenoids) into a wide variety of unsymmetrical zirconacycles has been determined. In all but one case a single regioisomer was obtained. A combination of steric and electronic effects is needed to explain the results and imply that the carbenoid is acting predominantly as an electrophilic species. The first carbenoid insertion into a zirconacyclopentadiene is noted.

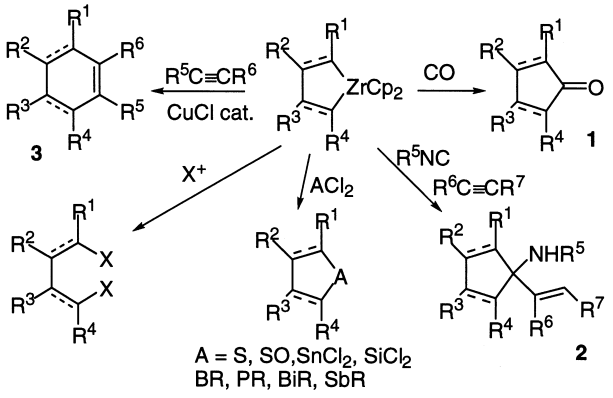
Introduction

The wide variety of zirconacycles available from simple organic precursors either by cocyclisation of 1,*n*-dienes, -enynes and -diynes using a zirconocene 'Cp_2Zr' equivalent, or by trapping of zirconocene η^2-alkene, -alkyne, and -benzyne complexes with alkenes or alkynes, make them attractive as intermediates in organic synthesis (Scheme 1).[1] Methods for further elaboration of these zirconacycles forming carbon–heteroatom bonds include oxygenation, halogenation,[2] and metathesis with a variety of elemento-dihalides 'ACl_2' (Scheme 2).[3] Carbon–carbon bond forming methods include carbonylation[4] to give **1** or, more recently tandem processes involving the insertion of isocyanides and trapping of the resulting zirconocene η^2–imine complexes with unsaturated species, for example alkynes to afford **2**.[5] Takahashi has developed a wide range of copper catalysed elaborations of zirconacycles including 1,1- and 1,2-additions to alkynes (e.g. to form **3**),[6] 1,1-additions to acid chlorides,[7] and addition to 1,2-, 1,3- or 1,4-dihalides.[8] All the above processes retain the symmetry of the starting zirconacycle so questions of regiochemistry of the addition do not occur.



Scheme 1. Formation of zirconacycles.

Processes in which the two carbon–zirconium bonds of the zirconacycle are differentially elaborated are also known including monohalogenation,[9] mixed dihalogenation,[10] addition of Ph_2PCl[9a] and R_3SnCl,[9] isocyanide insertion,[5c,9b,11] addition of aldehydes, ketones and nitriles[1a,12] and copper catalysed addition of acid chlorides, enones, and allyl-, aryl- and alkynyl-halides.[13] We have recently shown that the insertion of metal carbenoids (R^1R^2CLiX) into zirconacycles provides many new pathways for elaboration. The insertion reaction of lithium chloroallylides **4** to afford σ,η^3-zirconacycles **6** which react with



Scheme 2. Elaboration of zirconacycles.

Keywords: zirconium; zirconacycle; carbenoid; insertion reactions.
* Corresponding author. Tel.: +44(0)2380-592777; fax: +44(0)2380-593781; e-mail: rjw1@soton.ac.uk

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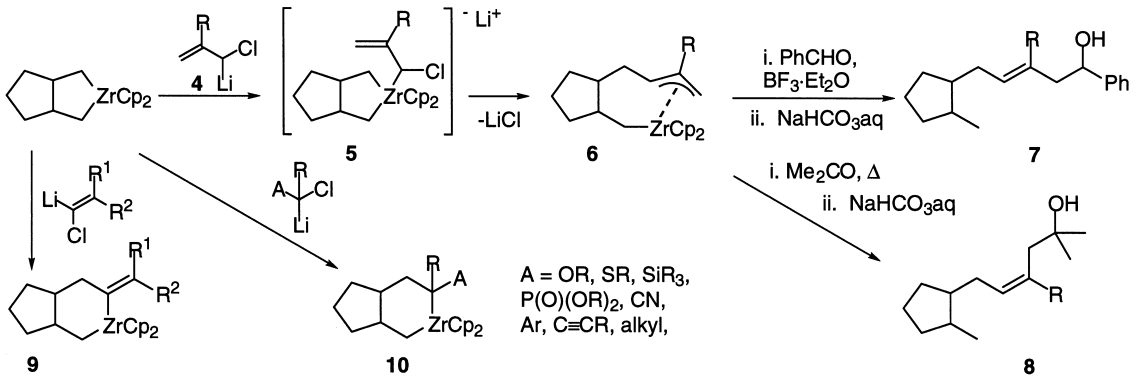
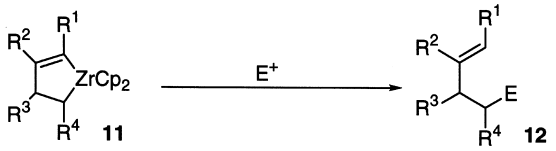


Scheme 3. Carbenoid insertion into zirconacycles.

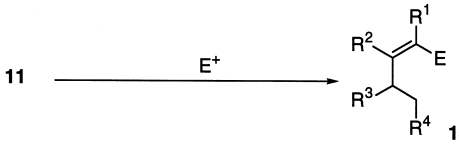
many electrophiles, for example aldehydes and ketones, to afford highly elaborated organic products **7** and **8** (Scheme 3) is particularly useful.[14] We have also shown that a wide variety of carbenoids allow ring expansion of zirconacyclopentanes and -pentenes to 6-member zirconacycles **9** and **10**, which in many cases may be further elaborated.[15] A reasonable mechanism for the carbenoid insertion is by initial donation of an electron pair to the 16-electron zirconium centre to form an 18-electron zirconate complex **5** followed by a 1,2-metallate rearrangement[16] (a process originally noted by Negishi for insertion into acyclic organozirconocene species).[17] For use in total synthesis it is important to be able to predict the regiochemistry of processes which differentially elaborate the two carbon–zirconium bonds of unsymmetrical zirconacycles.

Selective insertion into zirconacyclopentenes (including zirconaindenes) **11** is known. Most relevant to the work described below is the regioselective insertion of isocyanides into the alkyl–zirconium bond to afford **12** (Eq. (1)).[5c,9b,11] Protonolysis (first site),[9b] addition of aldehydes, ketones and nitriles,[1a,12] trimethyltin chloride,[9b] and halogenolysis with CBr_4 or CCl_3Br[9b] also occur into the alkyl–zirconium bond. For protonation and oxygen insertion this selectivity has been demonstrated for the case R^1=H.[4f] Halogenolysis with I_2 or Br_2 generally gives initial attack on the vinyl–zirconium bond to afford **13** on hydrolysis (Eq. (2)).[9b] When the vinyl bond carries a phenyl substituent the selectivity is reversed.[9b] Copper catalysed functionalisation of zirconacyclopentenes generally occurs first at the vinyl–zirconium bond to give **13**.[7b,13a,b] In summary, direct attack on the carbon–metal bond of zirconacyclopentenes occurs on the alkyl side. Where the reagents may first complex with, or add to, the double bond (halogens, organocopper species), the selectivity is usually reversed.



(1)

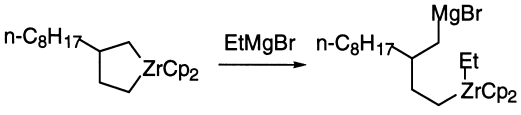
E^+(E) = H_2O (H), RNC (CHO), Me_3SnCl ($SnMe_3$), O_2 (OH), I_2 (R^1=Ar) (I), CBr_4 (Br), RCHO (RCHOH).



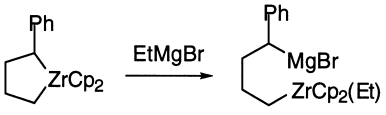
(2)

E^+ = Allyl chloride, benzoyl chloride or enones with a Cu catalyst. I_2 when $R^1 \neq$ Ar.

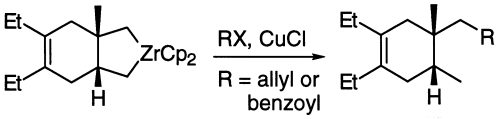
Most of the published examples of differential elaboration of the two carbon–zirconium bonds of saturated zirconacycles use symmetric systems where regiocontrol is not relevant. Takahashi and Negishi showed that magnesium/zirconium exchange of monocyclic zirconacyclopentanes was selective for the bond closest to a β-substituent (Eq. (3)) or for the bond adjacent to an α-phenyl substituent (Eq. (4)).[18] Copper catalysed allylation or benzoylation followed a similar selectivity (Eqs. 5 and 6).[13c] The mechanism of a catalytic cyclomagnesiation reported by Mori implies that an intermediate zirconacycle undergoes selective transmetallation as shown in Eq. (7).[19,20]



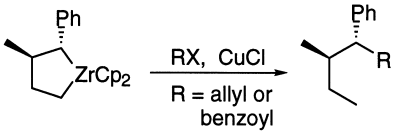
(3)



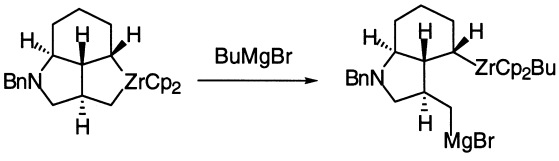
(4)



(5)



(6)



(7)

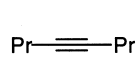
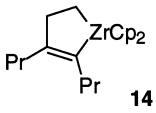
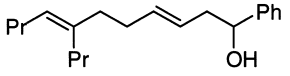
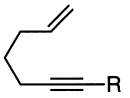
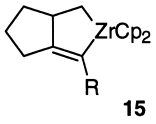
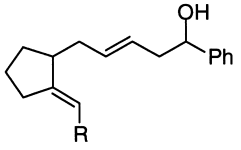
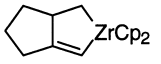
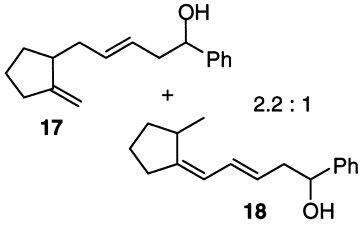
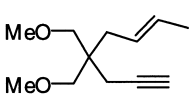
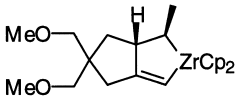
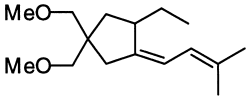
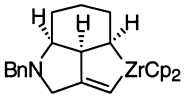
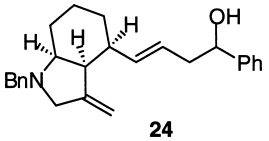
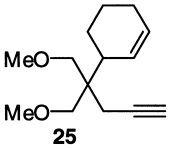
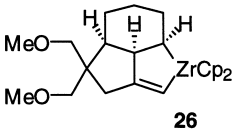
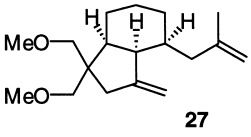
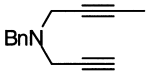
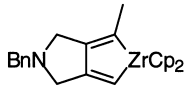
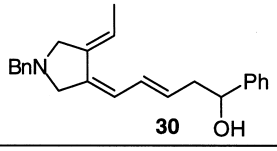
In this paper we report our studies on the regiochemistry of insertion of lithium chloroallylides into zirconacycles.[21]

Results

We have already reported that the insertion of lithium chloroallylide into mono- and bi-cyclic zirconacyclopentenes **14** and **15** derived from disubstituted alkynes (R≠H, Table 1, entries 1 and 2) is completely selective for the alkyl–zirconium bond.[14e] The selectivity might be electronically or sterically derived, a question which could be probed with a substrate unsubstituted on the vinyl–carbon (R=H). Cyclisation of terminal alkynes with the Negishi reagent [zirconocene(1-butene), generated in situ from dibutylzirconocene] fails,[22] but reaction of 1,6-heptenyne with zirconocene(ethylene), followed by heating[23] gave the zirconacycle **16**. Insertion of lithium chloroallylide followed by benzaldehyde gave a 2.2:1 mixture of regioisomeric insertion products **17** and **18**, favouring insertion into the alkyl–zirconium bond (Table 1, entry 3).

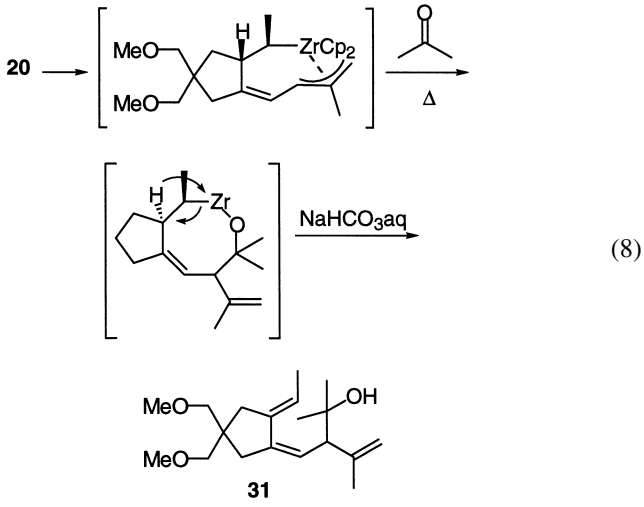
In an effort to shift the regioselectivity of insertion entirely towards the vinyl–zirconium bond we examined zirconacyclopentenes where the alkyl carbon attached to the

Table 1. Carbenoid insertions into unsaturated zirconacycles

Entry	Starting Material	Zirconacycle[a]	Elaboration Method[b]	Product(s)	Yield
1		 **14**	A		90%[c]
2		 **15**	A	 R: Ph 55%[c]; $SiMe_3$ 69%[c]; nBu 91%[c]	
3		 **16**	A	 **17** + **18**	2.2 : 1 79%
4	 **19**	 **20**	B	 **21**	66%
5	 **22**	 **23**	A	 **24**	28%
6	 **25**	 **26**	C	 **27**	78%
7	 **28**	 **29**	D	 **30**	76%

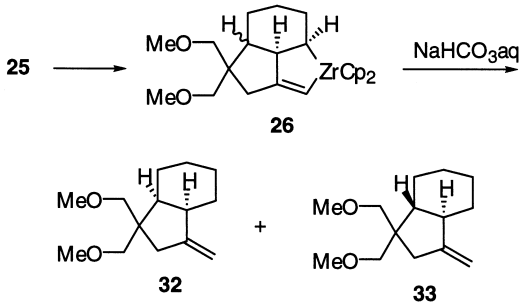
[a] Zirconacycles in entry 1 were formed from the alkyne and zirconocene(ethylene) (Ref. 9b), in entries 3, 5 and 7 by reaction with zirconocene(ethylene) followed by thermolysis (Ref. 23), in entries 4 and 6 by reaction with Cp_2ZrCl_2/Mg (Ref. 24) and in entry 2 by reaction with zirconocene(1-butene) (Ref. 1).
[b] Method A: (i) lithium chloroallylide; (ii) aldehyde, $BF_3.OEt_2$; (iii) aq. $NaHCO_3$. Method B: (i) lithium chloromethallylide; (ii) AcOH. Method C: (i) lithium chloromethallylide; (ii) $NaHCO_3$aq. Method D. As A but 5 equiv. lithium chloroallylide, PhCHO and $BF_3.Et_2O$ used.
[c] Ref. 14e.

metal carried extra substitution. Co-cyclisation of substrate **19** containing a *trans*-1,2-disubstituted alkene and a terminal alkyne using zirconocene dichloride and magnesium (recently reported conditions which are compatible with terminal alkynes[24]) gave zirconacycle **20**. High yielding insertion of lithium chloromethallylide required removal of residual magnesium salts by filtration. Presumably rapid transmetallation of the lithium chloromethallylide was giving a unreactive magnesium species. Protonation of the product of insertion of lithium chloromethallylide into **20** with glacial acetic acid gave the product **21** derived entirely from insertion into the vinyl–zirconium bond (Table 1, entry 4). Protonation with $NaHCO_3$aq. gave a mixture of double bond positional isomers. Insertion of acetone unexpectedly gave the product **31** (Eq. (8)) from addition to the internal carbon of the allyl-system, rather than the previously exclusively observed terminal addition.[14a,b] β-Hydride elimination has also occurred from the presumed intermediate oxazirconacycle to give the observed triene **31**. Although a single isomer, the double bond stereochemistries in **31** have not been proven. *syn*-β-Hydride elimination would give the (*Z*)-ethylidene stereochemistry, but calculations indicate that this would be very unstable with respect to the (*E*)-ethylidene form shown and isomerisation during isolation and purification is likely. Addition of aldehydes to **20** induced by $BF_3{\cdot}Et_2O$ gave an inseparable mixture of products.



(8)

We next examined the cyclohexene derived zirconacycle **23** (formed by a different route by Barluenga[4f]). Much to our surprise, addition of lithium chloroallylide gave only the product of insertion into the alkyl–zirconium bond, albeit in poor yield (Table 1, entry 5). To rule out additional effects of the nitrogen atom we also examined the all carbon analogue **26**, formed as a 9:2 mixture of diastereoisomers by co-cyclisation of the enyne **25** using Cp_2ZrCl_2/Mg. Protonation of **26** gave a separable mixture of the octahydroindenes **32** and **33** (Eq. (9)). The relative stereochemistry of **32** and **33** was based on NMR, in particular small coupling constants to the ring junction allylic C–H in the major isomer **32**. Further elaboration of **26** was problematic and only by performing the carbenoid insertion at low temperature (−100°C), and quenching the reaction at −78°C with methanol could we obtain high yields of the carbenoid insertion product **27**. The result confirmed the selectivity for the more hindered alkyl–zirconium bond noted with **23**. The carbenoid insertion product **27** was obtained as a single isomer, despite the diastereoisomeric mixture of zirconacycles.

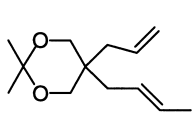
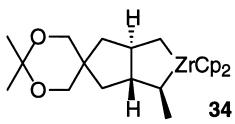
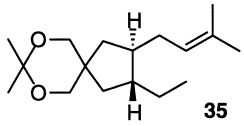
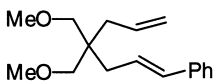
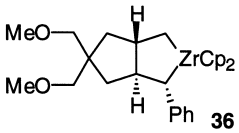
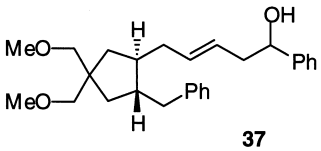
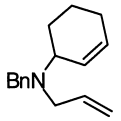
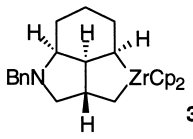
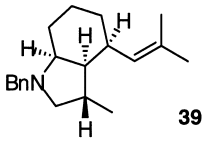
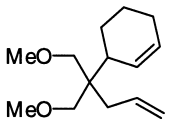
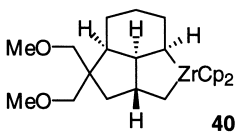
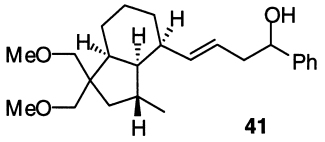
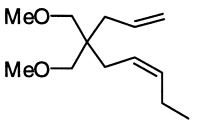
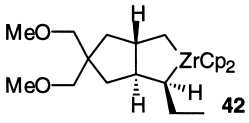
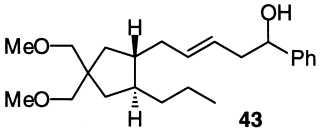
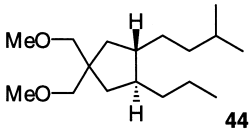


(9)

Successful insertion into vinyl–zirconium bonds in Table 1, entries 3 and 4, prompted us to examine reactions with a suitable zirconacyclopentadiene substrate. Co-cyclisation of **28** using Cp_2ZrCl_2/Mg gave the zirconacyclopentadiene **29**. We were delighted to find that insertion of lithium chloroallylide followed by benzaldehyde gave an excellent yield of the interesting triene **30** (Table 1, entry 7), although 5 equiv. of the carbenoid were needed for optimum yield.

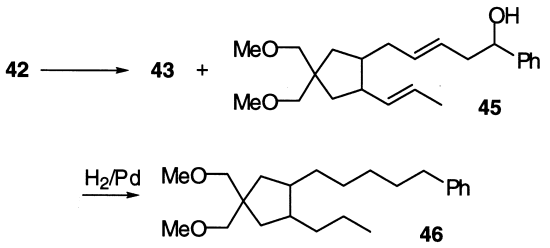
Insertions into zirconacyclopentanes were next examined. Zirconacycles **34** and **36** derived from *trans*-alkenes carrying terminal methyl, or phenyl substituents inserted lithium chloroallylides exclusively into the less hindered side (Table 2, entries 1 and 2). Insertion into saturated zirconacycles **38** (previously reported by Mori[25]) and **40** derived from co-cyclisation of a terminal alkene and a cyclohexene occurred exclusively into the more hindered side (Table 2, entries 3 and 4), as was observed with enyne derived systems **23** and **26**. The stereochemistry of **40** follows from the precedent of **38**, and close similarities in the NMR spectra of the products **41** and **27**. Whether the dramatic change in regioselectivity between entries 1 and 2, and 3 and 4 of Table 2 is due to the alkene geometry, or its incorporation in a cyclohexene ring was examined with the zirconacycle **42** derived from an acyclic *cis*-disubstituted alkene. Insertion of lithium chloroallylide followed by benzaldehyde occurred exclusively into the less hindered side (Table 2, entry 5) but the product **43** was contaminated with the dehydrozirconation product **45** (Eq. (10)). If the reaction of the allyl complex with benzaldehyde was left at room temperature for two days **45** became the almost exclusive product (72%). By carrying out the reaction with benzaldehyde for 2 h at room temperature **43** could be isolated containing <10% of **45**. For full characterisation the mixture was hydrogenated to give **46** as a single compound (Eq. (10)). Similarly insertion of lithium chloromethallylide into **42** followed by hydrolysis with $NaHCO_3$aq. gave a mixture of alkene regioisomers which afforded the single compound **44** on hydrogenation. A conclusion from the regioselective insertion into **42** is that the unexpected regioselectivity of Table 2, entries 3 and 4 (and by implication, Table 1, entries 5 and 6) is due to the

Table 2. Carbenoid insertions into α-substituted saturated zirconacycles

Entry	Starting Material	Zirconacycle[a]	Elaboration method[b]	Product	Yield
1		 **34**	B	 **35**	87%
2		 **36**	A	 **37**	45%
3		 **38**	B	 **39**	66%
4		 **40**	A	 **41**	79%
5		 **42**	A	 **43**	80%
6		**42**	C	 **44**	80%

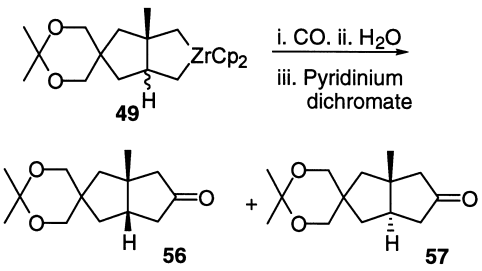
[a] Zirconacycles were formed by reaction with zirconocene(1-butene) (Ref. 1).
[b] Method A: (i) lithium chloroallylide; (ii) benzaldehyde, $BF_3{\cdot}OEt_2$; (iii) $NaHCO_3$ aq. Method B: (i) lithium chloromethallylide; (ii) $NaHCO_3$ aq. Method C: as B, then H_2/PtO_2.

cyclohexyl ring, rather than alkene geometry.



(10)

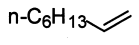
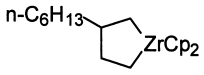
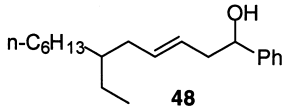
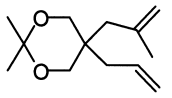
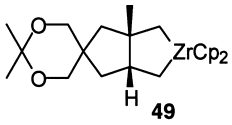
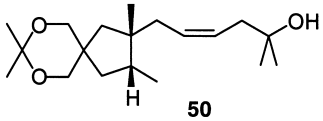
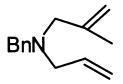
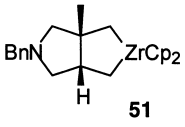
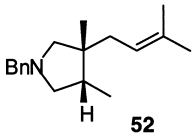
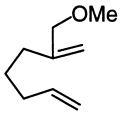
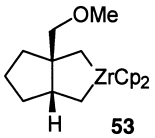
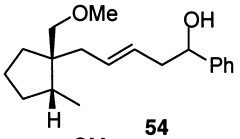
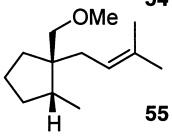
Finally we examined saturated zirconacyclopentanes where the difference between the two carbon–zirconium bonds is in a substituent β to the metal (Table 3). With the monocyclic zirconocycle **47** insertion occurred exclusively into the side closest to the β-substituent to give an excellent yield of **48** (Table 3, entry 1). The bicyclic zirconacyclopentane **49** carrying a methyl substituent at the ring junction (i.e. β-to the metal) gave the same result—carbenoid insertion occurs exclusively into the 'more hindered' side to afford **50** after addition of acetone (Table 3, entry 2). This regiochemical result has been used in the total synthesis of the dolabellane diterpene natural product acetoxyodontoschismenol.[14d,26] Both the zirconacycle **49**, and the final product **50** contained 20% of the isomer resulting from formation of the *trans*-fused zirconacycle (the exclusive isomer in all-carbon systems lacking the ring-junction methyl group). The formation of the *cis*-fused isomer as the major stereoisomer of **49** was proven by carbonylation to afford the cyclopentanones **56** and **57** (Eq. (11)). *Cis* and *trans* assignments were based on the close agreement of ring junction methyl proton NMR resonances (*cis*, 1.14; *trans*, 0.82) with that of the known 1-methyl-bicyclo[3.3.0]-3-octanone (*cis*, 1.18; *trans*, 0.75).[27]



(11)

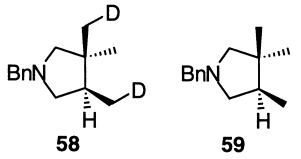
Co-cyclisation of *N*-allyl-*N*-benzyl-*N*-(2-methylallyl)amine with zirconocene gave the zirconacycle **51** exclusively as the *cis*-fused isomer. The stereochemistry of **51** was proven

Table 3. Carbenoid insertions into β-substituted saturated zirconacycles

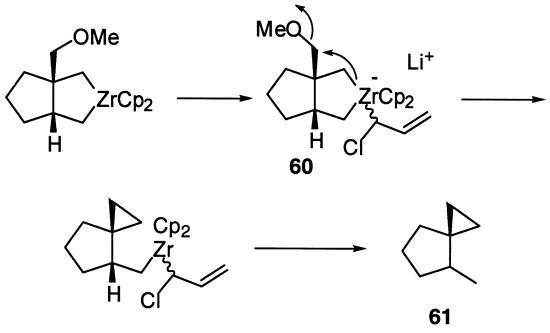
Entry	Starting Material	Zirconacycle[a]	Elaboration method[b]	Product	Yield
1		 **47**	A	 **48**	89%
2		 **49**	C	 **50**	49%[c]
3		 **51**	B	 **52**	40%[d]
4		 **53**	A	 **54**	27%
5		**53**	B	 **55**	36%

[a] Zirconacycles were formed by reaction with zirconocene(1-butene) (Ref. 1) except entry 1 which was formed by reaction with zirconocene(ethylene) (Ref. 18).
[b] Method A: (i) lithium chloroallylide; (ii) benzaldehyde, $BF_3{\cdot}OEt_2$; (iii) $NaHCO_3$ aq. Method B: (i) lithium chloromethallylide; (ii) $NaHCO_3$ aq. Method C: (i) lithium chloroallylide; (ii) acetone, 56°C, 24 h; (iii) $NaHCO_3$ aq.
[c] Zirconacycle and product contain 20% of *trans*-fused isomer.
[d] Plus 40% protonated zirconacycle.

by quenching with D_2O to give **58** in which the carbon-13


58 **59**

NMR shift of the deuterated methyl group on a quaternary centre (22.8) was shifted upfield compared to the undeuterated one (28.4) by steric compression ('γ-*gauche* effect'[28]). Insertion of lithium chloromethylallylide into **51** was incomplete, the product **59** of protonation of **51** being recovered, but was exclusively into the side nearest the β-substituent. We also examined the zirconacycle **53** carrying a CH_2OMe substituent on the ring junction to investigate possible electronic effects (inductively electron withdrawing rather than donating like Me) (Table 3, entries 4 and 5). Interestingly the zirconacycle **53** was formed exclusively *cis*-fused, proven by protonolysis and correlation to the known ((1*S*, 2*S*)-1,2-dimethylcyclopentyl)methanol.[29] For **53** insertion of lithium chloroallylide occurred into the carbon–zirconium bond closest to the extra substituent (Table 3, entries 4) and gave **54** in low yield after insertion of benzaldehyde. Insertion of lithium chloromethallylide followed by protonation gave the product **55** with the same regiocontrol and slightly better yield. The low yields of **54** and **55** arose in the carbenoid insertion step. Protonation of the intermediate zirconacycle **53** gave the expected product in high yield. We may speculate that an 'ate' complex **60** may eliminate the OMe group to form a volatile cyclopropane **61** (Eq. (12)) and an effect on the observed regiochemistry cannot be ruled out.


60 **61** (12)

Discussion

The above regioselectivity results obtained for the insertion

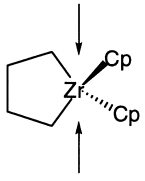


Figure 1. Lateral attack.

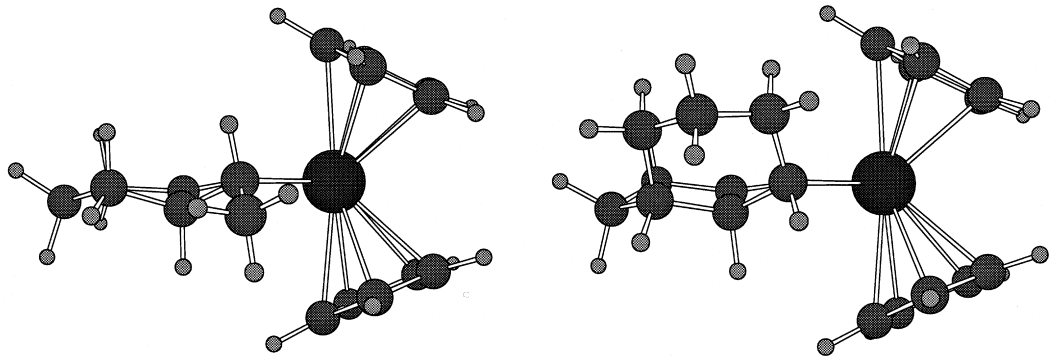
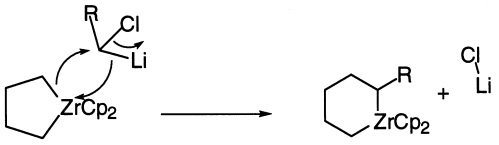
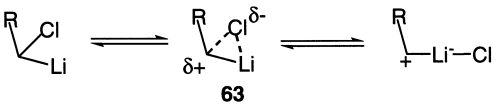


Figure 2. Side views of **20** and **26** (CH_2OMe substituents replaced by H).

of lithium chloroallylide or chloromethallylide into zirconacycles do not have a simple explanation. The selectivity is probably kinetically derived since the insertions occur in less than 5 min at −85°C. The insertion mechanism (via an 'ate' complex **5**) suggested in Scheme 3 implies initial nucleophilic attack of the carbenoid at the metal centre. The empty zirconium centred orbital upon which such attack should occur exists in the σ-ligand plane, and lateral attack is expected (Fig. 1). It has been demonstrated both experimentally and theoretically that this direction of attack occurs with carbon-monoxide.[30] Steric hindrance of attack then provides a reasonable explanation for the regioselectivity displayed in Table 1, entries 1–4 and 7, and Table 2, entries 1, 2, 5 and 6. In the particular case of insertion into **16** (Table 1, entry 3) the vinyl C–H adjacent to the zirconium lies in the plane of the LUMO, whereas the $Zr–CH_2$ hydrogens lie above and below the plane and provide less steric hindrance to the lateral attack. The dramatic reversal in selectivity observed in Table 1 between entry 4 and entries 5 and 6 is more difficult to explain. The cyclohexane ring in **23** and **26** holds the 'CH_2' nearest the metal well away from the plane of the LUMO whereas the methyl group in **20** is in the plane (Fig. 2) so a change in selectivity towards insertion in the alkyl side might be expected. However, the alkyl side is bulkier in **23/26** than in **16** so a further factor is needed to explain the change in selectivity from 1:0 to 2.2:1 between Table 1, entries 3 and 5/6. The unexpected regioselectivity caused by the fused cyclohexyl ring is clearly seen in Table 2, entries 3 and 4 where insertion occurs into the more sterically hindered side of **38** and **40**. In search of an explanation we carried out geometry optimisation and molecular orbital calculations on the model **62** using the ZINDO program (theoretical INDO/1 parameters[31]), as implemented in the CAChe workstation.[32] The most stable starting conformations of the zirconacycle for the calculations were determined using MM2 calculations keeping the $ZrCp_2$ fragment (taken from the crystal structure of *trans*-2,2-bis(η^5-cyclopentadienyl)-2-zircona-perhydropentalene)[32] rigid. We were disappointed to find that the LUMO of **62** showed no significant differences in coefficients either side of the metal (Fig. 3). In comparison the HOMO showed a much larger coefficient on the C–Zr bond into which insertion occurs (Fig. 3). The NHOMO showed the opposite relative sizes of coefficients for the two C–Zr bonds, but was calculated to be 140 kJ mol^{-1} lower in energy than the HOMO and should therefore have less influence. Using the sum of all valence orbitals to generate an electron density isosurface (0.01 $eÅ^{-3}$), coloured using Fukui's frontier electron density,[33] the susceptibility towards nucleophilic attack showed no difference between the two sides of **32**, but for electrophilic attack, again we observed a marked bias towards the cyclohexyl side (Fig. 3). The implication is that the mechanism suggested in Scheme 3 with initial attack by a nucleophilic species to form an 'ate' complex may not be correct. Rapid reversible formation of a zirconate complex (like **5**) with the 1,2-metallate rearrangement being rate and product determining is possible but difficult to investigate experimentally or theoretically. The unexpected regiochemistry of insertion into **23**, **26**, **38**, and **40** is more consistent with initial attack by an electrophilic species. A concerted insertion into the C–Zr bond seems most likely since calculations show that the zirconium centre is strongly electrophilic (Eq. (13)). Both calculations and experimental results demonstrate that 1-chloro-1-lithio species are powerful electrophiles through 'metal assisted ionisation' (Eq. (14)).[34] The lowest energy structure of some 1-halo-1-lithium species may be represented as **63**, with a substantial positive charge on the carbenoid carbon. It is interesting that in a similar system to **38** Mori observes the opposite regiochemistry for transmetallation with alkylmagnesium species (Table 2, entry 3, cf. Eq. (7), notwithstanding the stereochemical difference).[19]



(13)



(14)

63

ZINDO calculations on the zirconacycles **20**, **29** and **34** demonstrated the same bias in the HOMO and the susceptibility towards electrophilic attack on the side of the methyl substituent. Presumably the steric blocking effect of the methyl group in these cases overrides the 'electronic bias'. The same dominance of steric effects applies to the zirconacycles **14** and **15**. It is interesting that in the zirconacycle **16** the HOMO shows little bias towards either carbon–zirconium bond and we get a mixture of regioisomeric

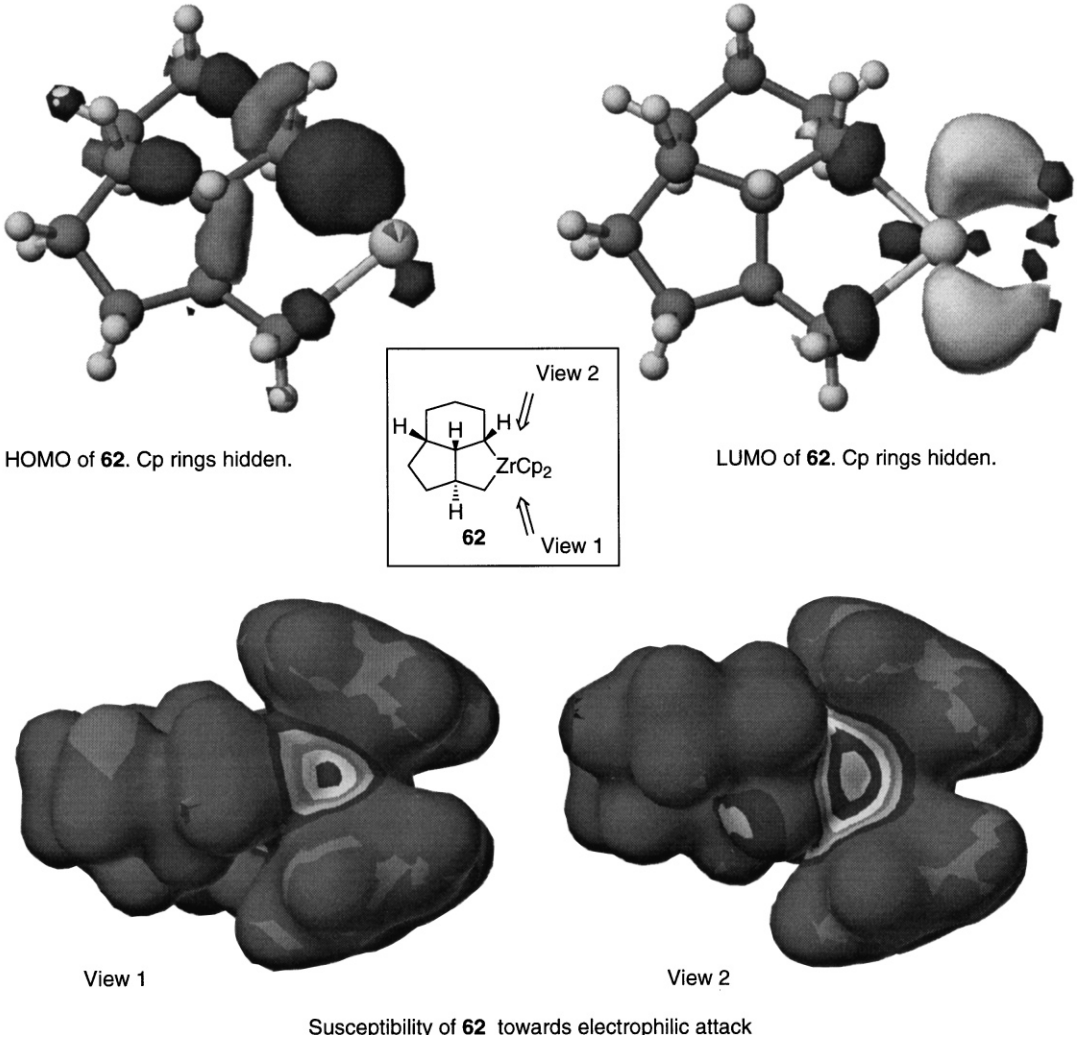


Figure 3. ZINDO calculations on **62**.

insertion products. The result for insertion into zirconacycle **42** (Table 2, entries 5 and 6) seems anomalous since ZINDO calculations show a strong preference for insertion into the carbon–zirconium bond adjacent to the ethyl substituent, and the ethyl group is orientated away from the direction of lateral attack. Molecular mechanics calculations on **42** indicate that the conformation A in which the terminal methyl group blocks attack on the metal is 6.9 kJ mol^{-1} lower in energy than conformation B (which more closely resembles the structure of the cyclohexyl-fused system **40**) (Fig. 4) overriding the electronic bias.

Zirconacycles where the symmetry breaking substituent is β- to the zirconium (Table 3) insert allyl carbenoids with excellent regiocontrol. Calculations show a slight bias of the HOMO towards the observed sites of insertion (Fig. 5). The LUMO again shows no significant differences between the two sides. The regioselectivity is the same as that observed

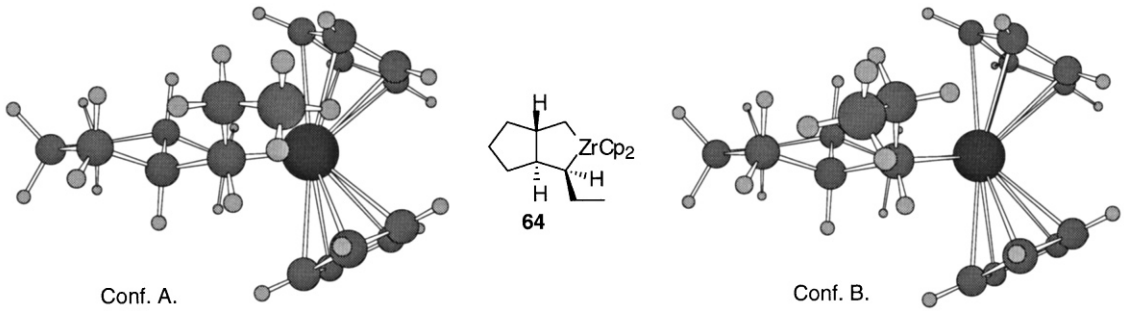


Figure 4. Conformations of a model **64** for **42** (CH_2OMe replaced by H).

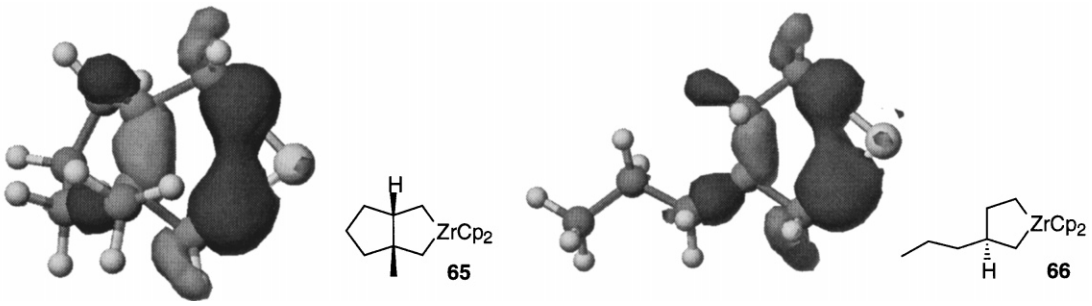


Figure 5. HOMOs for **65** and **66**, models for **49** and **47**, respectively. Cp rings hidden.

in related systems for transmetallations with organomagnesium and organocopper species (Table 3, entry 1, cf. Eq. (3) and entries 2/3, cf. Eq. (5)).[18,13c] ZINDO calculations indicate that the oxygen substitution in zirconacycle **53** has little effect on the HOMO—there is a slight bias towards the observed site of insertion.

Conclusion

In summary we have uncovered a complex pattern of regioselectivity in the insertion of carbenoids into zirconacycles. It is pleasing that in all but one case examined so far insertion is completely regioselective. Steric hindrance of attack on one side of the zirconacycle provides a reasonable explanation in only some cases. Theoretical calculations provide an explanation of the regiocontrol in other cases only if the dominant Frontier Molecular Orbital interaction is between the LUMO of the carbenoid and HOMO of the zirconacycle. These regioselectivity results suggest that addition of lithium chloroallylides to zirconacycles should be considered as a concerted insertion of an electrophilic carbenoid into a carbon–zirconium bond, rather than nucleophilic attack on the metal to form a zirconate species followed by a 1,2-metallate rearrangement.

Experimental

General techniques

Molecular modelling (MM2) and semi-empirical (ZINDO) calculations were carried out using CAChe Worksystem Software version 4.0 (Oxford Molecular) running on a PowerMac 7600 computer. Molecular orbital surfaces are shown at the 0.06 $e\text{Å}^{-3}$ contour. Electron density surfaces are shown at the 0.01 $e\text{Å}^{-3}$ contour and coloured using Frontier Density.[33]

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC300 spectrometer (300 MHz proton, 75 MHz carbon) in $CDCl_3$ unless otherwise stated. The chemical shifts in proton spectra are reported as values in ppm relative to internal tetramethylsilane standard, or residual solvent. The following abbreviations are used to denote multiplicity and shape of signal and may be compounded: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Carbon-13 spectra were proton decoupled and referenced to solvent and signals reported as s, d, t, q, depending on the number of directly attached protons (0,1,2,3, respectively), this being determined by DEPT experiments. Electron impact (70 eV) (EI), Chemical Ionisation (using ammonia as the reagent gas) (CI), and electrospray (ES) mass spectra, including accurate masses, were recorded on a VG Analytical 70–250-SE double focusing mass spectrometer. Atmospheric pressure chemical ionisation (APCI) mass spectra were recorded on a VG Platform spectrometer in acetonitrile. *M/z* signals are reported as values in atomic mass units followed by the peak intensity relative to the base peak. Infrared spectra were recorded on a Perkin–Elmer 1600 FT-IR spectrometer as films between sodium chloride plates unless otherwise stated. Peaks are described as s (strong), m (medium), w (weak), and/or br (broad). Elemental analyses were performed by the University College London Microanalysis Service. Melting points were measured on a Gallenkamp type apparatus and are uncorrected. Organometallic reactions were performed under argon using standard Schlenk techniques. Tetrahydrofuran was freshly distilled from sodium/benzophenone. Petrol refers to the fraction of petroleum ether that has a boiling range 40–60°C and was distilled before use.

Synthesis of cyclisation precursors

General procedure for synthesis of malonate derived precursors. Sodium (0.74 g, 30 mmol) was added portionwise to ethanol (25 mL). Once dissolution was complete a solution of diethyl allylmalonate (4.00 g, 20 mmol) or dimethyl propargylmalonate (3.40 g, 20 mmol) in ethanol (10 mL) was added slowly. After 10 min a solution of the appropriate allyl or propargyl bromide (25 mmol) in ethanol (10 mL) was added dropwise. The mixture was stirred at room temperature overnight, then poured onto water (250 mL) and extracted with diethyl ether (3×100 mL). The combined extracts were washed with water (3×200 mL) and brine (200 mL), dried ($MgSO_4$) and the solvent removed in vacuo to afford the dialkylated malonate. In some cases purification was unnecessary, in others purification was by column chromatography on silica eluted with 5% diethyl ether in petrol.

To a suspension of lithium aluminium hydride (2.28 g, 60 mmol) in diethyl ether (100 mL) at 0°C was added dropwise a solution of the substituted malonate ester formed above, in diethyl ether (50 mL). The reaction was left to stir overnight at room temperature. The reaction was quenched by dropwise addition of a solution of ethyl acetate (10 mL) in diethyl ether (40 mL) followed by water

(10 mL). The mixture was poured onto 2 M HCl solution (500 mL) and the organic layer separated. The aqueous layer was extracted with diethyl ether (2×250 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed in vacuo to give a diol as a clear, thick oil.

Sodium hydride (1.60 g of a 60% suspension in oil, 40 mmol) was placed in a flask under nitrogen, washed with hexane (20 mL), and then suspended in anhydrous THF (20 mL). A solution of the diol formed above in THF (50 mL) was added dropwise over 30 min, followed by a solution of methyl iodide (40 mmol, 2.49 mL) in THF (20 mL). After 2 h the reaction was quenched by addition of methanol (10 mL) then poured onto water (300 mL) and extracted with diethyl ether (3×100 mL). The combined extracts were washed with water (3×100 mL) and brine (100 mL), dried ($MgSO_4$) and the solvent removed in vacuo to give a yellow oil. Purification was by column chromatography on silica eluted with 5% diethyl ether in petrol, followed by Kugelrohr distillation. Using the above method the following materials were prepared.

(*E*)-4,4-Bis(methoxymethyl)-6-octen-1-yne (19). The title compound was prepared as above, using 'predominantly *trans*' commercial crotyl bromide. Final Kugelrohr distillation (100–110°C at 1.0 mmHg) gave a clear, colourless oil (74% of a 1:5.9 *Z*/*E* ratio by GC). Data is given for the *trans* isomer: ^{1}H NMR: δ 5.29–5.60 (2H, m), 3.284 (6H, s), 3.16–3.22 (4H, m), 2.133 (2H, d, J=2.8 Hz), 2.043 (2H, d, J=7.4 Hz), 1.934 (1H, t, J=2.8 Hz), 1.137 (3H, dd, J=7.4, 0.9 Hz) ppm. ^{13}C NMR: δ 128.67 (d), 125.98 (d), 81.49 (s), 74.58 (2t), 70.13 (d), 59.30 (2q), 41.90 (s), 34.80 (t), 22.00 (t), 18.18 (q) ppm. IR: 1606 (w), 1477 (m), 1457 (m), 1437 (m), 1196 (s), 1109 (s), 970 (s), 632 (s) cm^{-1}. LRMS (APCI): 197.2 (41%, M+H$^+$), 183.1 (64), 152.9 (32). Anal. Found: C, 72.93; H, 10.42. $C_{12}H_{20}O_2$ requires C, 73.43; H, 10.27%.

3-(1,1-Bis(methoxymethyl)-3-butynyl)-1-cyclohexene (25). Obtained as a pale yellow oil after chromatography (52%). Final purification by Kugelrohr distillation was not possible due to unexpected thermal instability. ^{1}H NMR: δ 5.65–5.80 (2H, m), 3.381 (2H, s), 3.374 (2H, s), 3.309 (6H, s), 2.45 (1H, m), 2.311 (2H, d, J=2.8 Hz), 1.957 (1H, t, J=2.8 Hz), 1.90–2.00 (2H, m), 1.72–1.83 (2H, m), 1.45–1.58 (2H, m) ppm. ^{13}C NMR: δ 128.77 (d), 128.06 (d), 82.20 (s), 74.71 (t), 74.55 (t), 70.15 (d), 59.42 (2q), 43.47 (s), 39.10 (d), 25.38 (t), 24.41 (t), 23.07 (t), 21.26 (t) ppm. IR: 2115 (w), 1448 (m), 1197 (m), 1110 (s), 637 (m) cm^{-1}. LRMS (APCI): 223.0 (M+H$^+$, 27%), 190.9 (M−MeOH+H$^+$, 87). HRMS (EI). Found M$^+$, 222.1614. $C_{14}H_{22}O_2$ requires: 222.1620.

(*E*)-4,4-Bis(methoxymethyl)-1-phenyl-1,6-heptadiene. Final Kugelrohr distillation (150–160°C, 0.5 mmHg) gave a clear, colourless oil (83%). ^{1}H NMR: δ 7.17–7.38 (5H, m), 6.418 (1H, d, J=15.8 Hz), 6.227 (1H, dt, J=15.8, 7.6 Hz), 5.85 (1H, m), 5.04–5.13 (2H, m), 3.336 (6H, s), 3.221 (4H, s), 2.223 (2H, d, J=7.3 Hz), 2.120 (2H, d, J=7.6 Hz) ppm. ^{13}C NMR (62.9 MHz): δ 137.87 (s), 134.40 (d), 132.67 (d), 128.47 (2d), 126.91 (d), 126.43 (d), 126.00 (2d), 117.60 (t), 75.22 (2t), 59.16 (2q), 42.45 (s), 36.89 (t), 35.86 (t) ppm. IR: 1639 (w), 1599 (w), 1449 (m), 1198 (m), 1109 (s), 968 (m), 914 (m), 745 (m), 694 (m) cm^{-1}. LRMS (EI): 260 (M$^+$, 78%), 228 (M$^+$−MeOH, 20), 196 (M$^+$−2MeOH, 17), 155 (34), 104 (22), 91 (62), 45 (100). HRMS (EI): Found: M$^+$, 260.1797. $C_{17}H_{24}O_2$ requires: 260.1776. Anal. Found: C, 77.9; H, 9.65. $C_{17}H_{24}O_2$ requires: C, 78.4; H, 9.29%.

3-(1,1-Bis(methoxymethyl)-3-butenyl)-1-cyclohexene. Final Kugelrohr distillation (110–120°C at 0.7 mmHg) gave a clear, colourless oil (67%). ^{1}H NMR: δ 5.876 (1H, ddt, J=16.9, 10.0, 7.5 Hz), 5.65–5.72 (2H, m), 5.006 (1H, d, J=16.9 Hz), 4.994 (1H, d, J=10.0 Hz), 3.319 (2H, s), 3.296 (3H, s), 3.282 (3H, s), 3.269 (2H, s), 2.36 (1H, m), 2.135 (2H, d, J=7.5 Hz), 1.92–1.98 (2H, m), 1.68–1.80 (2H, m), 1.39–1.55 (2H, m) ppm. ^{13}C NMR: δ 135.80 (d), 128.52 (d), 128.33 (d), 116.83 (t), 75.42 (t), 75.28 (t), 59.27 (q), 59.24 (q), 43.55 (s), 38.87 (d), 36.64 (t), 25.46 (t), 24.17 (t), 23.16 (t) ppm. IR: 1637 (m), 1480 (m), 1447 (s), 1197 (s), 1163 (m), 1107 (s), 998 (m), 970 (m), 911 (s), 721 (m) cm^{-1}. LRMS (APCI): 225.0 (M+H$^+$, 100%), 192.9 (M−MeOH+H$^+$, 80). Anal. Found: C, 74.65; H, 10.86. $C_{14}H_{24}O_2$ requires: C, 74.95; H, 10.78%.

(*Z*)-4,4-Bis(methoxymethyl)-1,6-nonadiene. (*Z*)-1-Bromopent-2-ene was prepared by the method of Corey[35] and used crude in the reaction sequences described above to afford the title diene (80%) as a clear, colourless oil after Kugelrohr distillation (110–125°C at 1 mmHg). ^{1}H NMR: δ 5.782 (1H, ddt, J=18.1, 9.2, 7.5 Hz), 5.446 (1H, dtt, J=11.0, 6.8, 1.2 Hz), 5.326 (1H, dtt, J=11.0, 7.2, 1.2 Hz), 4.98–5.06 (2H, m), 3.275 (6H, s,), 3.134 (4H, s), 2.00–2.08 (6H, m), 0.931 (3H, t, J=7.5 Hz) ppm. ^{13}C NMR: δ 134.61 (d), 134.23 (d), 123.97 (d), 117.53 (t), 75.13 (2t), 59.17 (2q), 42.14 (s), 36.75 (t), 29.57 (t), 20.57 (t), 14.36 (q) ppm. IR: 1638 (m), 1477 (s), 1458 (s), 1197 (s), 1178 (s), 1118 (s), 995 (m), 973 (m), 914 (s), 734 (m) cm^{-1}. LRMS (APCI): 213.2 (M+H$^+$, 100%). Anal. Found: C 73.14; H, 11.32. $C_{13}H_{24}O_2$ requires: C, 73.54; H, 11.39%.

Preparation of other cyclisation precursors

***N*-Benzyl-*N*-(2-cyclohexen-1-yl)-*N*-(2-propynyl)amine (22).** A solution of benzylamine (10 g, 93 mmol), propargyl bromide (2.9 g, 24 mmol) and potassium carbonate (38 g, 279 mmol) in acetonitrile (50 mL) was stirred at room temperature for 36 h. The reaction solution was then poured into distilled water (150 mL) and the organic products extracted with diethyl ether (200 mL). The organic portion was washed with water (3×100 mL) and brine (2×100 mL) and dried over $MgSO_4$. Removal of solvent and distillation (70°C, 1 mmHg) gave *N*-(prop-2-ynyl)-benzylamine[36] (1.57 g, 45%). To a suspension of potassium carbonate (4.4 g, 32 mmol) in acetonitrile (40 mL) was added *N*-(prop-2-ynyl)-benzylamine (1.5 g, 10.3 mmol) and 3-bromocyclohexene (1.58 mL, 13.7 mmol) and the solution was stirred at room temperature for 48 h. The reaction solution was then poured into water (150 mL) and the organic products extracted with diethyl ether (150 mL). The organic portion was washed with water (3×100 mL), brine (2×100 mL) and dried over anhydrous $MgSO_4$. Removal of solvent and Kugelrohr distillation (140°C at 0.1 mmHg) gave the title compound as a colourless oil (2.242 g, 95%). ^{1}H NMR: δ 7.45–7.30 (5H, m), 5.95–5.84 (2H, m), 3.94 (1H, d, J=13.6 Hz), 3.75 (1H, d,

J=13.6 Hz), 3.58 (1H, m), 3.41 (1H, d, J=2.4 Hz), 3.40 (1H, d, J=2.4 Hz), 2.26 (1H, t, J=2.4 Hz), 2.15–1.55 (6H, m) ppm. ^{13}C NMR: δ 139.80 (s), 130.51 (d), 130.16 (d), 128.83 (d, 2C), 128.29 (d, 2C), 126.95 (d), 81.45 (s), 72.44 (d), 57.56 (d), 53.13 (t), 39.29 (t), 25.36 (t), 24.90 (t), 31.34 (t) ppm. IR: 3296 (s), 2356 (w), 1648 (w), 1601 (w), 1492 (m), 1451 (s), 1144 (s), 1122 (s), 740 (s), 698 (s) cm^{-1}. LRMS (ES): 226 (M+H$^+$, 100%), 150 (20). HRMS (EI): Found: M$^+$, 225.1502. $C_{16}H_{19}N$ requires: 225.1517.

***N*-Benzyl-*N*-(2-butynyl)-*N*-(2-propynyl)amine (28).** To a suspension of potassium carbonate (4.4 g, 32 mmol) in acetonitrile (40 mL) was added *N*-(prop-2-ynyl)-benzylamine (1.5 g, 10.3 mmol, prepared as described above) and 2-butynyl *p*-toluenesulphonate (Lancaster, 3.3 g, 13.7 mmol). The solution was stirred at room temperature for 48 h. The reaction solution was then poured into distilled water (150 mL) and the organic products extracted with diethyl ether (150 mL). The combined organic phases were washed with water (3×100 mL), brine (2×100 mL) and dried over anhydrous $MgSO_4$. Removal of solvent and Kugelrohr distillation (120°C at 0.1 mmHg) gave the title compound as a colourless oil (1.368 g, 67%). ^{1}H NMR: δ 7.42–7.25 (5H, m), 3.71 (2H, s), 3.45 (2H, d, J=2.4 Hz), 3.39 (2H, q, J=2.2 Hz), 2.30 (1H, t, J=2.4 Hz), 1.87 (3H, t, J=2.4 Hz) ppm. ^{13}C NMR: δ 138.04 (s), 129.26 (d, 2C), 128.38 (d, 2C), 127.35 (d), 80.80 (s), 78.96 (s), 74.26 (s), 73.25 (d), 57.18 (t), 42.44 (t), 41.67 (t), 3.61 (q) ppm. IR: 3288 (s), 2231 (w), 1602 (m), 1494 (s), 1453 (s), 1359 (s), 1327 (s), 1128 (s), 1074 (s), 971 (s), 741 (s), 699 (s) cm^{-1}. LRMS (ES): 198 (M+H$^+$, 100%), 150 (10%). HRMS (EI): Found: M$^+$, 197.1189. $C_{14}H_{15}N$ requires: 197.1204.

2-(Methoxymethyl)-1,6-heptadiene. 2-Hydroxymethyl-1,6-heptadiene[37] was prepared by $LiAlH_4$ reduction of the sodium salt of diethyl 4-pentenylmalonate and contained 20% of the over reduced compound 2-hydroxymethyl-6-heptene. To a solution of 2-hydroxymethyl-1,6-heptadiene (3.2 mmol, 0.504 g of ca. 80% pure compound) in dry CH_2Cl_2 (10 mL) at −50°C was added triethylamine (6 mmol, 0.83 mL) and methanesulphonyl chloride (5 mmol, 0.40 mL). The reaction was warmed to −20°C over 4 h, then poured onto water (100 mL) and extracted with CH_2Cl_2 (100 mL). The organic extract was dried ($MgSO_4$) and the solvent removed in vacuo to give the crude methanesulphonate as a yellow oil, which was dissolved in methanol (5 mL) and added to a solution of sodium (16.7 mmol, 0.40 g) in methanol (20 mL). The reaction was stirred at room temperature overnight then poured onto water (200 mL), and extracted with diethyl ether (3×100 mL). The combined extracts were washed with water (3×100 mL) and brine (100 mL), dried ($MgSO_4$) and the solvent removed in vacuo to give the crude title product as a yellow oil. Purification by column chromatography (silica, 5% diethyl ether in petrol), followed by Kugelrohr distillation (100–105°C at 10 mmHg) gave the title compound (0.356 g, 80%) as a colourless oil. ^{1}H NMR: δ 5.809 (1H, ddt, J=17.1, 10.3, 6.6 Hz), 5.004 (1H, d, J=17.1 Hz), 4.999 (1H, s), 4.954 (1H, d, J=10.3 Hz), 4.905 (1H, s), 3.847 (2H, s), 3.308 (3H, s), 2.03–2.10 (4H, m), 1.550 (2H, pentet, J=7.6 Hz) ppm. ^{13}C NMR: δ 145.96 (s), 138.73 (d), 114.75 (t), 111.62 (t), 75.68 (t), 57.94 (q), 33.58 (t), 32.58 (t), 26.95 (t) ppm. IR: 1641 (s), 1451 (s), 1192 (s), 1109 (s), 992 (m), 908 (s) cm^{-1}. LRMS (APCI): 141.0 (M+H$^+$, 100%). Anal. Found: C, 76.79; H, 11.78. $C_9H_{16}O$ requires: C, 77.09; H, 11.50%.

Formation and elaboration of zirconacycles

Method A. Co-cyclisation using Cp_2ZrCl_2/2 EtMgCl. To a stirred solution of zirconocene dichloride (0.292 g, 1 mmol) in THF (5 mL) under argon at −80°C was added ethylmagnesium bromide (0.64 mL of a 3.2 M solution in diethyl ether, 2 mmol) and the reaction stirred at this temperature for 40 min before the enyne or diyne (1 mmol) in THF (2 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature over 1 h, then heated at 60°C for 5 h to afford the required zirconacycle as a solution in THF.

Method B. Co-cyclisation using Cp_2ZrCl_2/Mg. To a suspension of magnesium powder (0.039 g, 1.5 mmol) in THF (1 mL) was added 1,2-dibromoethane (0.30 mL of a 0.5 M solution in THF, 0.15 mmol). The mixture was stirred at room temperature for 30 min then the solvent removed in vacuo. A solution of the enyne (1 mmol) in THF (4 mL) was added and the reaction mixture cooled to 0°C under argon. A solution of zirconocene dichloride (0.322 g, 1.1 mmol) in THF (6 mL) was added dropwise over 30 min. Over 3 h the reaction changed colour through yellow to a deep brown. The reaction solution was filtered through a sinter under argon to remove excess magnesium powder, giving the zirconacycle as a solution in THF.

Method C. Co-cyclisation using in situ generated zirconocene(1-butene). To a solution of zirconocene dichloride (0.293 g, 1 mmol) in THF (5 mL) under argon at −78°C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2 mmol) followed by a solution of the appropriate diene (1 mmol) in THF (1 mL). The reaction mixture was allowed to warm to room temperature overnight to give the zirconacycle as a solution in THF.

Method D. Insertion of lithium chloroallylide or lithium chloromethyallylide into a zirconacycle with protic work-up. The zirconacycle solution was cooled to −78°C and allyl chloride or methallyl chloride (1.5 mmol) was added followed by the dropwise addition of a solution of lithium diisopropylamide [1.5 mmol, prepared from *n*-BuLi (0.60 mL of a 2.5 M solution in hexanes, 1.5 mmol) and diisopropylamine (0.152 g, 1.5 mmol) in THF (2 mL) at 0°C for 30 min]. The reaction was warmed to room temperature over 2 h before quenching by addition of methanol (2 mL) and saturated sodium bicarbonate solution (5 mL). After stirring for 30 min the reaction mixture was poured onto water (50 mL) and extracted with diethyl ether (3×25 mL). The combined extracts were washed with water (3×50 mL) and brine (50 mL), dried ($MgSO_4$), and the solvent removed in vacuo to afford the crude product.

Method E. Sequential insertion of lithium chloroallylide or lithium chloromethyallylide and benzaldehyde into a zirconacycle. The zirconacycle solution was cooled to −78°C and allyl chloride or methallyl chloride (1.5 mmol) was added followed by the dropwise addition of a solution of lithium 2,2,6,6-tetramethylpiperidide [1.5 mmol,

prepared from *n*-BuLi (0.60 mL of a 2.5 M solution in hexanes, 1.5 mmol) and 2,2,6,6-tetramethylpiperidine (0.212 g, 1.5 mmol) in THF (2 mL) at 0°C for 30 min]. The reaction was warmed to −30°C over 2 h, then cooled to −78°C and benzaldehyde (0.20 mL, 2 mmol,) and $BF_3{\cdot}OEt_2$ (0.29 mL, 2 mmol) were added. After 15 min at −78°C the reaction was allowed to warm to room temperature over 5 h. Methanol (2 mL) and saturated sodium bicarbonate solution (2 mL) were added and the mixture stirred for 1 h, then poured onto water (50 mL) and extracted with diethyl ether (3×50 mL). The combined extracts were washed with water (3×100 mL), brine (50 mL), dried ($MgSO_4$) and the solvent removed in vacuo to afford the crude product.

(*E*)-5-(2-Methylenecyclopentyl)-1-phenyl-3-penten-1-ol (17) and (3*E*,5*Z*)-5-(2-methylcyclopentylidene)-1-phenyl-3-penten-1-ol (18). Co-cyclisation of hept-1-en-6-yne[4c] using method A and elaboration of the zirconacycle using method E (allyl chloride) followed by column chromatography (silica, 8% diethyl ether in petrol) gave the title compounds as a clear yellow oil in a combined yield of 79% (0.191 g). Ratio of products **17**:**18**, determined from ^{1}H NMR of the crude product to be 2.2:1. ^{1}H NMR: δ 7.40–7.15 (5H, m), 6.32 (1H(**18**), m), 5.90 (1H(**18**), dd, *J*=11.0, 1.7 Hz), 5.65–5.40 (2H(**17**)+1H(**18**), m), 4.91(1H(**17**), br. s), 4.80 (1H(**17**), br. s), 4.75–4.65 (1H(**17**)+1H(**18**), m), 2.85 (1H(**17**), m), 1.65–1.15 (11H(**17**)+10H(**18**), m), 1.02 (3H(**18**), d, *J*=7.0 Hz) ppm. ^{13}C NMR: δ 156.33 (s), 152.06 (s), 144.12 (s, 2C), 133.67 (d), 131.66 (d), 128.50 (d, 4C), 127.55 (d, 2C), 126.88 (d), 125.98 (d, 4C), 120.11 (d, 2C, **18**), 104.69 (t, **17**), 73.81 (d, **18**), 73.56 (d, **17**), 43.78 (d, **17**), 43.16 (t), 43.04 (t), 37.67 (t), 35.40 (d, 18), 35.01 (t), 33.70 (t), 33.51 (t), 32.40 (t), 24.29 (t), 23.98 (t), 21.26 (q, **18**) ppm. IR: 3362 (br. s), 1649 (m), 1602 (w), 1492 (m), 1451 (s), 1047 (m), 969 (s), 699 (s) cm^{-1}. LRMS (EI): 242 (M^+, 4%), 225 (M^+−OH, 25), 143 (25), 136 (100), 121 (15), 107 (66), 79 (42). HRMS (EI): Found: M^+, 242.1677. $C_{17}H_{22}O$ requires: 242.1671.

(4*Z*)-3-Ethyl-1,1-bis(methoxymethyl)-4-(3-methyl-2-butenylidene)cyclopentane (21). (*E*)-4,4-Bis(methoxymethyl)-6-octen-1-yne **19** was co-cyclised using method B, and the zirconacycle elaborated using method D (methallyl chloride), except that protonolysis was carried out with glacial acetic acid (2 mL) for 24 h. The crude product was purified by column chromatography (silica, 5–10% diethyl ether in petrol) to give the title diene **21** as a colourless oil (0.167 g, 66%). ^{1}H NMR: δ 6.072 (1H, d, *J*=11.5 Hz), 5.892 (1H, d, *J*=11.5 Hz), 3.353 (3H, s,), 3.307 (3H, s), 3.25–3.37 (4H, m), 3.131 (1H, d, *J*=10.9 Hz), 3.094 (1H, d, *J*=10.9 Hz), 2.66 (1H, m), 2.298 (1H, d, *J*=15.5 Hz), 2.149 (1H, d, *J*=15.5 Hz), 1.791 (3H, s), 1.733 (3H, s), 1.22–1.37 (2H, m), 0.889 (3H, t, *J*=8.1 Hz) ppm. ^{13}C NMR: δ 146.27 (s), 132.21 (s), 121.92 (d), 118.57 (d), 77.70 (t), 74.93 (t), 59.48 (q), 59.42 (q), 46.59 (s), 41.06 (t), 40.67 (d), 37.53 (t), 29.66 (t), 26.43 (q), 18.16 (q), 11.96 (q) ppm. IR: 1622 (w), 1476 (m), 1458 (m), 1377 (m), 1198 (m), 1112 (s), 734 (s) cm^{-1}. LRMS (APCI): 252.3 (M^+, 9%), 221.2 (M−MeOH+H^+, 100), 189.1 (M−2MeOH+ H^+, 18).

3((*Z*)-((2*E*)-2-Ethylidene-4,4-bis(methoxymethyl)cyclopentylidene)methyl)-2,4-dimethyl-4-penten-2-ol (31). The zirconacycle **30** was prepared from (*E*)-4,4-bis(methoxymethyl)-6-octen-1-yne **19** via method B and lithium chloromethallylide inserted as in method D. The solvent was then removed in vacuo and replaced with benzene (5 mL). The reaction mixture was filtered through an in-line sinter under argon and the residue extracted with more benzene (3 mL). The resulting solution was concentrated in vacuo to 1 mL and dry acetone (1 mL) added. The resulting mixture was heated at 50°C overnight. After cooling to room temperature methanol (2 mL) and saturated sodium bicarbonate solution (2 mL) were added. The mixture was stirred for 1 h, then poured onto water (50 mL) and extracted with diethyl ether (3×50 mL). The combined extracts were washed with water (3×100 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed in vacuo. Purification by column chromatography (silica, 10–20% diethyl ether in petrol) gave the title compound (0.148 g, 51%) as a colourless oil. ^{1}H NMR: δ 5.913 (1H, dt, *J*=10.7, 2.5 Hz), 5.860 (1H, qt, *J*=6.0, 2.6 Hz), 4.86 (2H, m), 3.317 (3H, s), 3.312 (3H, s), 3.225 (1H, d, *J*=11.2 Hz), 3.228 (1H, d, *J*=10.1 Hz), 3.202 (1H, d, *J*=11.2 Hz), 3.198 (1H, d, *J*=10.1 Hz), 2.912 (1H, d, *J*=10.7 Hz), 2.328 (1H, dd, *J*=16.0, 2.3 Hz), 2.22–2.27 (2H, m), 2.229 (1H, dd, *J*=16.0, 2.3 Hz), 1.795 (3H, dd, *J*=1.4, 0.9 Hz), 1.660 (3H, dt, *J*=7.0, 1.5 Hz), 1.195 (3H, s), 1.185 (3H, s) ppm. OH not seen. ^{13}C NMR: δ 146.18 (s), 141.32 (s), 139.98 (s), 116.98 (d), 114.31 (d), 113.74 (t), 76.03 (t), 75.84 (t), 72.95 (s), 59.42 (q), 59.39 (q), 57.58 (d), 45.05 (s), 36.34 (t), 25.95 (t), 28.44 (q), 28.08 (q), 23.13 (q), 14.85 (q) ppm. IR: 3456 (s, br), 1637 (m), 1449 (s), 1374 (s), 1198 (s), 1112 (s), 954 (m), 910 (m), 734 (s) cm^{-1}. LRMS (APCI): 331.3 (M+Na^+, 9%), 309.3 (M+H^+, 16), 291, (M−H_2O+H^+, 100), 259.2 (M−H_2O−MeOH+H^+, 41%). HRMS (EI). Found: M^+, 308.2345. $C_{19}H_{32}O_3$ requires: 308.2345.

***rac*-(3*E*)-4-(3a*S*,4*S*,7a*S*)-1-Benzyl-3-methyleneoctahydro-1*H*-indol-4-yl)-1-phenyl-3-buten-1-ol (24).** *N*-Benzyl-*N*-(2-cyclohexen-1-yl)-*N*-(2-propynyl)amine (**22**) was co-cyclised using method A, and the zirconacycle elaborated using method E except that 5 equiv. of allyl chloride/LiTMP and $PhCHO/BF_3{\cdot}Et_2O$ were used. The crude product was purified by column chromatography (grade III basic Al_2O_3, 50% diethyl ether in petrol) to afford the title compound as an orange oil (0.108 g, 28%). ^{1}H NMR: δ 7.45–7.10 (10H, m), 6.06 (1H, dt, *J*=15.5, 7.6 Hz), 5.32 (1H, m), 4.95 (1H, br. d, *J*=7.8 Hz), 4.80 (1H, br. d, *J*=7.8 Hz), 4.55 (1H, m), 3.74 (1H, dd, *J*=13.2, 4.1 Hz), 3.35–3.25 (2H, m), 3.17 (1H, dd, *J*=13.2, 5.9 Hz), 2.96 (1H, ddt, *J*=14.5, 6.2, 2.3 Hz), 2.76–2.61 (2H, m), 2.45–2.20 (3H, m), 1.75–1.05 (6H, m) ppm. ^{13}C NMR: δ 149.79 (s), 145.19 (s), 140.06 (s), 138.54 (d), 137.99 (d), 128.84 (d, 2C), 128.57 (d, 2C), 128.46 (d, 2C), 127.29 (d), 127.14 (d), 126.20 (d, 2C), 105.56 (t), 73.72 (d), 62.84 (d), 58.68 (t), 57.19 (t), 48.02 (d), 43.14 (t), 41.50 (d), 28.49 (t), 23.99 (t), 19.83 (t) ppm. IR: 3392 (s, br), 1666 (m), 1602 (s), 1494 (m), 1453 (s), 1377 (m), 1046 (m), 970 (m), 699 (s) cm^{-1}. LRMS (ES): 374 (M+H^+, 100%). HRMS (EI): Found: M^+, 373.2390. $C_{26}H_{31}ON$ requires: 373.2406.

***rac*-(3a*R*,4*S*,7a*S*)-1,1-Bis(methoxymethyl)-3-methylene-4-(2-methyl-2-propenyl)octahydro-1*H*-indene (27).** 3-(1,1-Bis(methoxymethyl)-3-butynyl)-1-cyclohexene **25** was co-cyclised using method B and the zirconacycle **26** elaborated

by method D (methallyl chloride) except that carbenoid addition was carried out at −100°C, and the reaction quenched below −60°C. Column chromatography (silica, 5% diethyl ether in petrol) followed by Kugelrohr distillation (155–160°C at 1 mmHg) gave the title compound (0.206 g, 74%) as a pale yellow oil. ^{1}H NMR: δ 4.960 (1H, d, *J*=2.6 Hz), 4.889 (1H, d, *J*=2.6 Hz), 4.748 (1H, s), 4.696 (1H, s), 3.360 (3H, s), 3.315 (3H, s), 3.24–3.42 (4H, m), 2.72–2.76 (1H, m), 2.22–2.36 (3H, m), 2.038 (1H, dd, *J*=17.0, 1.3 Hz), 1.74–1.82 (3H, m), 1.733 (3H, s), 1.04–1.56 (5H, m) ppm. ^{13}C NMR: δ 149.63 (s), 144.81 (s), 111.27 (t), 107.41 (t), 75.19 (t), 73.86 (t), 59.35 (q), 59.17 (q), 46.84 (d), 46.14 (s), 45.13 (d), 43.25 (t), 39.16 (t), 37.54 (d), 26.62 (t), 26.47 (t), 23.78 (t), 22.52 (q) ppm. IR: 1650 (m), 1497 (m), 1447 (s), 1198 (s), 1112 (s), 910 (s), 888 (s), 734 (s) cm^{-1}. LRMS (APCI): 279.2 (M+H$^+$, 9%), 247.2, (M−MeOH+H$^+$, 100), 215.1 (M−2MeOH+H$^+$, 36). Anal. Found: C, 77.39; H, 10.96. $C_{18}H_{30}O_2$ requires: C, 77.65; H, 10.86%.

***rac*-(3a*R*,7a*S*)-1,1-Bis(methoxymethyl)-3-methyleneoctahydro-1*H*-indene (32) and *rac*-(3a*S*,7a*S*)-1,1-bis(methoxymethyl)-3-methyleneoctahydro-1*H*-indene (33).** The zirconacycle **26** was prepared from 3-(1,1-bis(methoxymethyl)-3-butynyl)-1-cyclohexene **25** via method B and quenched at room temperature by addition of methanol (2 mL) and saturated sodium bicarbonate solution (5 mL). After 30 min the reaction mixture was poured onto water (50 mL) and extracted with diethyl ether (3×25 mL). The combined extracts were washed with water (3×50 mL), brine (50 mL), dried ($MgSO_4$), and the solvent removed in vacuo to give a yellow oil which was purified by column chromatography (silica, CH_2Cl_2) to afford **32** (0.156 g, 70%) and **33** (35 mg, 16%). Data for **32**: ^{1}H NMR: δ 4.901 (1H, tdd, *J*=3.1, 2.0, 0.9 Hz), 4.768 (1H, qd, *J*=2.6, 1.1 Hz), 3.331 (3H, s), 3.308 (3H, s), 3.21–3.37 (4H, m), 2.733 (1H, br s), 2.323 (1H, ddt, *J*=17.6, 2.3, 1.2 Hz), 2.081 (1H, dq, *J*=17.6, 2.3 Hz), 1.925 (1H, ddt, *J*=16.9, 5.0, 2.6 Hz), 1.837 (1H, dt, *J*=11.5, 6.5 Hz), 1.46–1.66 (3H, m), 1.33–1.41 (1H, m), 1.242 (1H, tq, *J*=3.3, 12.7 Hz), 1.111 (1H, ddq, *J*=2.1, 3.2, 12.2 Hz), 0.940 (1H, dq, *J*=3.2, 12.2 Hz) ppm. ^{13}C NMR: δ 151.58 (s), 104.94 (t), 74.93 (t), 73.95 (t), 59.37 (q), 59.23 (q), 47.39 (s), 42.69 (d), 41.87 (d), 37.08 (t), 25.75 (t), 25.12 (t), 24.14 (t), 21.21 (t) ppm. IR: 1656 (m), 1478 (m), 1448 (s), 1197 (s), 1110 (s), 964 (s), 913 (m), 873 (s) cm^{-1}. LRMS (APCI): 225.1 (M+H$^+$, 6%), 193.0 (M−MeOH+H$^+$, 100) Data for **33**: ^{1}H NMR: δ 4.724 (1H, dtd, *J*=2.4, 2.1, 1.4 Hz), 4.665 (1H, qd, *J*=2.6, 1.4 Hz), 3.327 (3H, s), 3.315 (3H, s), 3.22–3.40 (4H, m), 2.427 (1H, ddt, *J*=17.3, 1.1, 2.6 Hz), 2.155 (1H, dddd, *J*=17.3, 2.6, 1.8, 0.6 Hz), 1.94–2.05 (2H, m), 1.73–1.85 (3H, m), 1.09–1.26 (4H, m), 1.04 (1H, m) ppm. ^{13}C NMR: δ 154.24 (s), 102.29 (t), 78.11 (t), 74.64 (t), 59.34 (q), 59.21 (t), 51.89 (d), 47.61 (d), 46.42 (s), 38.57 (t), 29.65 (t), 27.82 (t), 26.97 (t), 26.10 (t) ppm. IR: 3068 (m), 2978 (s), 2921 (s), 2850 (s), 1657 (s), 1476 (m), 1446 (s), 1392 (w), 1257 (w), 1196 (s), 1110 (s), 963 (m), 872 (m) cm^{-1}. LRMS (APCI): 225.1 (M+H$^+$, 3%), 193.0 (M−MeOH+H$^+$, 100). Anal. (on mixture). Found: C, 75.23; H, 10.96. $C_{14}H_{24}O_2$ requires: C, 74.95; H, 10.78%.

***rac*-(3*E*,5*E*)-5-((4*Z*)-1-Benzyl-4-ethylidenepyrrolidinylidene)-1-phenyl-3-penten-1-ol (30).** *N*-Benzyl-*N*-(2-butynyl)-*N*-(2-propynyl)amine **28** was co-cyclised using method A, and the zirconacycle elaborated using method E except that 5 equiv. of allyl chloride/LiTMP and PhCHO/BF_3·Et_2O were used. The crude product was purified by column chromatography (grade III basic Al_2O_3, 50% diethyl ether in petrol) to afford the title compound as an orange oil (0.265 g, 76%). ^{1}H NMR: δ 7.40–7.05 (10H, m), 6.78 (1H, dd, *J*=14.8, 11.8 Hz), 5.91–5.80 (2H, m), 5.61 (1H, dt, *J*=15.2, 7.5 Hz), 4.45 (1H, dd, *J*=7.3, 5.5 Hz), 3.48 (2H, s), 3.26 (2H, s), 3.20 (2H, s), 2.46 (2H, m,), 1.41 (3H, d, *J*=7.2 Hz) ppm. OH not observed. ^{13}C NMR: δ 143.92 (s), 138.51 (s), 137.55 (s), 136.26 (s), 130.69 (d), 130.15 (d), 128.90 (d, 2C), 128.40 (d, 2C), 128.31 (d, 2C), 127.52 (d), 127.17 (d), 125.86 (d, 2C), 121.26 (d), 120.97 (d), 73.66 (d), 61.78 (t), 60.71 (t), 58.07 (t), 42.98 (t), 15.53 (q) ppm. IR: 3392 (m, br.), 1667 (m), 1602 (m), 1493 (m), 1451 (s), 1320 (m), 752 (s), 699 (s) cm^{-1}. LRMS (ES): 346 (M+H$^+$, 100%). HRMS (EI): Found: M$^+$, 345.2088. $C_{24}H_{27}ON$ requires: 345.2093.

***rac*-(2*R*,3*R*)-2-Ethyl-8,8-dimethyl-3-(3-methyl-2-butenyl)-7,9-dioxa-spiro[4.5]decane (35).** 5-Allyl-5-((*E*)-2-butenyl)-2, 2-dimethyl-1, 3-dioxane was co-cyclised according to the method C, and the zirconacycle elaborated using method D (methallyl chloride). Column chromatography (silica, 5% ether in petrol) followed by Kugelrohr distillation (142°C, 0.1 mmHg) gave the title compound as a colourless oil (0.231 g, 87%). ^{1}H NMR: δ 5.101 (1H, t septet, *J*=7.2, 1.5 Hz), 3.545 (4H, m), 2.221 (1H, ddd, *J*=14.3, 7.2, 4.4 Hz), 1.908 (1H, dd, *J*=13.2, 7.1 Hz), 1.838 (1H, dd, *J*=13.4, 7.2 Hz), 1.754 (1H, *J*=14.9, 7.9 Hz), 1.693–1.600 (2H, m), 1.672 (3H, s), 1.580 (3H, s), 1.398 (2H, m), 1.398 (6H, s), 0.982 (2H, m), 0.875 (3H, t, *J*=7.4 Hz) ppm. ^{13}C NMR: δ 131.81 (s), 123.28 (d), 97.71 (s), 70.42 (t), 70.39 (t), 46.03 (d), 45.01 (d), 40.08 (t), 39.82 (t), 39.66 (s), 32.14 (t), 26.89 (t), 25.97 (q), 24.23 (q), 23.76 (q), 17.91 (q), 12.70 (q) ppm. IR: 1651 (w), 1452 (m), 1385 (s), 1199 (s), 1078 (m), 1032 (m), 832 (m) cm^{-1}. LRMS (CI, NH_3): 284 (M+NH_4^+, 2%), 267 (M+H$^+$, 100), 251 (34), 209 (57), 191 (59). HRMS (EI): Found: M$^+$, 266.2223. $C_{17}H_{30}O_2$ requires: 266.2246.

***rac*-(3*E*)-(1*R*,2*R*)-(2-Benzyl-4,4-bis(methoxymethyl)cyclopentyl)-1-phenyl-3-penten-1-ol (37).** (*E*)-4,4-Bis(methoxymethyl)-1-phenyl-1,6-heptadiene was co-cyclised using method C, and the zirconacycle elaborated using method E (allyl chloride). Column chromatography (silica, 10–25% diethyl ether in petrol) gave the title compound (0.177 g, 45%) as a colourless oil. ^{1}H NMR: δ 7.11–7.34 (10H, m), 5.558 (1H, dt, *J*=14.8, 6.6 Hz), 5.398 (1H, dt, *J*=14.8, 6.6 Hz), 4.69 (1H, m), 3.316 (3H, s), 3.250 (3H, s), 3.162 (1H, d, *J*=13.8 Hz), 3.144 (1H, d, *J*=13.8 Hz), 3.112 (1H, d, *J*=13.8 Hz), 3.095 (1H, d, *J*=13.8 Hz), 2.894 (1H, dd, *J*=17.7, 3.9 Hz), 2.39–2.35 (2H, m), 2.306 (2H, dd, *J*=9.3, 13.2 Hz), 2.048 (1H, d, *J*=3.0 Hz), 1.855 (1H, m), 1.75–1.67 (2H, m), 1.52–1.62 (2H, m), 1.04–1.15 (2H, m) ppm. ^{13}C NMR (62.9 MHz): δ 144.09 (s), 141.61(s), 133.33 (d), 128.66 (2d), 128.35 (2d), 128.17 (2d), 127.39 (s), 126.53 (s), 125.83 (2d), 125.66 (d), 77.85 (t), 77.77 (t), 73.50 (s), 59.18 (2q), 46.22 (d), 45.11 (s), 44.76 (d), 42.76 (t), 40.31 (t), 39.14 (t), 38.70 (t), 36.71(t) ppm. IR: 3436 (s, br), 1603 (w), 1494 (m), 1453(s), 1266 (m), 1199 (m), 1108 (s), 967 (s), 739 (s), 701 (s) cm^{-1}.

LRMS (CI, NH_3): 426 ($M+NH_4^+$, 50%), 408 (M^+, 37), 391 ($M-H_2O+H^+$, 40), 359 ($M-H_2O-MeOH+H^+$, 100), 327 ($M-H_2O-2MeOH+H^+$, 91). HRMS (EI): Found: $(M+H)^+$, 409.2739. $C_{27}H_{37}O_3$ requires 409.2743.

***rac*-(3*S*,3a*S*,4*S*,7a*S*)-1-Benzyl-3-methyl-4-(2-methyl-1-propenyl)-octahydro-1*H*-indole (39).** *N*-Allyl-*N*-benzyl-*N*-(2-cyclohexen-1-yl)amine[19] was co-cyclised using method C and the zirconacycle elaborated using method D (methallyl chloride). Column chromatography (silica, 50% diethyl ether in petrol) gave the title compound (0.187 g, 66%) as a yellow oil. ^{1}H NMR: δ 7.22–7.40 (5H, m), 5.116 (1H, d, J=9.5 Hz), 3.709 (1H, d, J=13.2 Hz), 3.626 (1H, d, J=13.2 Hz), 2.96 (1H, m), 2.917 (1H, t, J=9.2 Hz), 2.57 (1H, m), 2.285 (1H, dd, J=5.2, 9.2 Hz), 2.16 (1H, m), 1.88–2.04 (2H, m), 1.54–1.79 (2H, m), 1.709 (3H, s), 1.645 (3H, s), 1.15–1.42 (3H, m), 1.025 (3H, d, J=6.6 Hz) ppm. ^{13}C NMR: δ 139.97 (s), 130.04 (s), 128.93 (d), 128.75 (2d), 128.26 (2d), 126.79 (d), 63.06 (d), 60.16 (t), 56.53 (t), 49.54 (d), 36.24 (d), 31.03 (d), 27.97 (t), 25.89 (q), 22.28 (q), 22.24 (t), 22.12 (t), 18.06 (q) ppm. IR: 1494 (m), 1452 (s), 1375 (m), 1264 (m), 909 (s), 735 (s), 699 (s) cm^{-1}. LRMS (ES): 284.3 ($M+H^+$, 100%). HRMS (EI): Found: M^+, 283.2299. $C_{20}H_{29}N$ requires: 283.2300.

***rac*-(*E*)-4-[(3*R*,3a*R*,4*S*,7a*S*)-1,1-Bis(methoxymethyl)-3-methyloctahydro-1*H*-inden-4-yl)-1-phenyl-3-buten-1-ol (41).** 3-(1,1-Bis(methoxymethyl)-3-butenyl)-1-cyclohexene was co-cyclised using method C and the zirconacycle elaborated using method E (allyl chloride). Column chromatography (silica, 10–25% diethyl ether in petrol) gave the title compound (0.294 g, 79%) as a pale yellow oil. ^{1}H NMR: δ 7.27–7.36 (5H, m), 5.627 (1H, dd, J=6.1, 15.6 Hz), 5.334 (1H, dt, J=15.6, 6.6 Hz), 4.68 (1H, m), 3.357 (3H, s), 3.305 (3H, s), 3.20–3.36 (4H, m), 2.46 (1H, m), 2.36 (1H, m), 2.198 (1H, d, J=3.1 Hz), 2.03 (1H, m), 1.91 (1H, m), 1.68–1.79 (3H, m), 1.46–1.54 (2H, m), 1.06–1.34 (5H, m), 0.948 (3H, d, J=6.5 Hz) ppm. ^{13}C NMR: δ 144.22 (s), 140.43 (d), 128.42 (2d), 127.48 (d), 125.92 (2d), 122.70 (d), 75.83 (t), 74.16 (t), 73.80 (d), 59.34 (q), 59.15 (q), 50.44 (d), 48.76 (s), 45.41 (d), 43.12 (t), 41.98 (d), 39.65 (t), 30.03 (d), 26.52 (t), 25.64 (t), 23.86 (q), 23.84 (t) ppm. IR: 3423 (s, broad), 1603 (w), 1493 (m), 1392 (m), 1376 (m), 1197 (s), 1158 (s), 1107 (s), 734 (s), 700 (s) cm^{-1}. LRMS (APCI+, no cone): 372.5 (M^+, 2%), 354.5 (M^+-H_2O, 3), 323.3 ($M-H_2O-MeOH+H^+$, 100), 291.2 ($M-H_2O-2MeOH+H^+$, 41). HRMS (EI): Found: $M-PhCHOH+H^+$, 266.2237. $C_{17}H_{30}O_2$ requires: 266.2246.

***rac*-(*E*)-5-[(1*S*,2*S*)-4,4-Bis(methoxymethyl)-2-propylcyclopentyl)-1-phenyl-3-penten-1-ol (43).** (*Z*)-4,4-Bis(methoxymethyl)-1,6-nonadiene was co-cyclised using method C and the zirconacycle elaborated using method E (allyl chloride) except that after addition of the benzaldehyde the reaction was warmed to 0°C over 2 h before quenching. Column chromatography (10–25% diethyl ether in petrol) gave the title compound (0.195 g, 54%) contaminated with <10% **45** as a colourless oil. ^{1}H NMR: δ 7.27–7.38 (5H, m), 5.550 (1H, dt, J=13.6, 6.6 Hz), 5.390 (1H, dt, J=13.6, 7.0 Hz), 4.682 (1H, br s), 3.343 (6H, s), 3.14–3.23 (4H, m), 2.41–2.47 (2H, m), 2.24–2.29 (2H, m), 1.65–1.84 (3H, m), 0.95–1.60 (8H, m), 0.892 (3H, t, J=7.1 Hz) ppm. ^{13}C NMR: δ 144.19 (s), 133.81 (d), 128.47 (2s), 127.49 (d), 126.38 (d), 125.96 (2d), 77.98 (2t), 73.61 (d), 59.38 (2q), 45.25 (s), 45.18 (d), 44.43 (d), 42.95 (t), 39.32 (t), 39.04 (t), 36.89 (t), 36.46 (t), 21.52 (t), 14.64 (q) ppm. IR: 3415 (s, br), 1453 (s), 1197 (m), 1108 (s), 1045 (m), 1026 (m), 965 (m), 700 (s) cm^{-1} LRMS (APCI): 343.4 ($M-H_2O+H^+$, 59%), 311.3 ($M-H_2O-MeOH+H^+$, 100), 279.3 ($M-H_2O-2MeOH+H^+$, 92). HRMS (EI): Found: $M-PhCHOH+H^+$, 254.2241. $C_{16}H_{30}O_2$ requires: 254.2245.

***rac*-(3*S*,4*S*)-3-(3-Methylbutyl)-1,1-bis(methoxymethyl)-4-propylcyclopentane (44).** (*Z*)-4,4-Bis(methoxymethyl)-1,6-nonadiene was co-cyclised using method C, and the zirconacycle elaborated using method D (methallyl chloride) to afford a crude product (0.227 g, 85%) as a mixture of double bond isomers. The alkene mixture was dissolved in CH_2Cl_2 (5 mL) and hydrogenated at 1000 psi in the presence of PtO_2 (10 mg) for 16 h. The reaction mixture was filtered through celite, solvent removed and the residue Kugelrohr distilled (150–155°C, at 1.0 mmHg) to give the title compound (0.227 g, 84%) as a colourless oil. ^{1}H NMR: δ 3.330 (6H, s), 3.14–3.20 (4H, m), 1.757 (1H, d, J=12.8 Hz), 1.735 (1H, d, J=12.8 Hz), 0.90–1.68 (13H, m), 0.872 (3H, t, J=8.0 Hz), 0.863 (3H, d, J=6.6 Hz), 0.840 (3H, d, J=6.6 Hz) ppm. ^{13}C NMR: δ 78.04 (2t), 59.38 (2q), 45.55 (d), 45.31 (s), 45.15 (d), 39.62 (t), 39.50 (t), 27.77 (t), 26.64 (t), 31.96 (t), 28.48 (d), 23.13 (q), 22.53 (q), 21.62 (t), 14.67 (q) ppm. IR (thin film) 1458 (s), 1384 (m), 1260 (m), 1198 (s), 1111 (s), 965 (m), 735 (m) cm^{-1}. HRMS (EI). Found: M^+, 270.2570. $C_{17}H_{34}O_2$ requires: 270.2559. Anal. Found: C, 75.13; H, 12.78. $C_{17}H_{34}O_2$ requires: C, 75.50; H, 12.67%.

***rac*-(*E*)-5-((1*S*,2*R*)-4,4-Bis(methoxymethyl)-2-((*E*)-1-propenyl)cyclopentyl)-1-phenyl-3-penten-1-ol (45).** (*Z*)-4,4-Bis(methoxymethyl)-1,6-nonadiene was co-cyclised using method C and the zirconacycle elaborated using method E (allyl chloride) except that after addition of the benzaldehyde the reaction was warmed to room temperature and stirred for 48 h, then quenched and worked up as normal. Column chromatography (10–25% diethyl ether in petrol) gave the title compound (0.258 g, 72%) contaminated with <5% **43** as a colourless oil. ^{1}H NMR: δ 7.27–7.37 (5H, m), 5.551 (1H, dt, J=15.1, 7.0 Hz), 5.33–5.47 (2H, m), 5.236 (1H, ddq, J=15.1, 7.9, 1.3 Hz), 4.67 (1H, m), 3.346 (6H, s), 3.23–3.16 (4H, m), 2.35–2.51 (2H, m), 2.26 (1H, m), 2.181 (1H, br s), 2.015 (1H, dddd, J=18.8, 16.0, 11.0, 7.7 Hz), 1.665 (3H, d, J=6.2 Hz), 1.50–1.81 (4H, m), 1.216 (1H, dd, J=13.1, 11.4 Hz), 1.038 (1H, dd, J=12.9, 11.2 Hz) ppm. ^{13}C NMR: δ 144.22 (s), 134.31 (d), 133.24 (d), 128.27 (2d), 127.28 (d), 126.40 (d), 125.90 (2d), 125.05 (d), 77.83 (t), 77.74 (t), 73.55 (d), 59.18 (2q), 48.59 (d), 45.31 (s), 45.13 (d), 42.77 (t), 39.82 (t), 38.51 (t), 36.37 (t), 18.04 (q) ppm. IR: 3417 (s, broad), 1452 (s), 1388 (m), 1197 (s), 1110 (s), 964 (s), 732 (s), 700 (s) cm^{-1}. LRMS (APCI): 341.4 ($M-H_2O+H^+$, 26%), 309.3 ($M-H_2O-MeOH+H^+$, 100), 277.3 ($M-H_2O-2MeOH+H^+$, 69). HRMS (EI): Found: $M-PhCHOH+H^+$, 252.2086. $C_{16}H_{28}O_2$ requires: 252.2089.

***rac*-(5-((1*S*,2*R*)-4,4-Bis(methoxymethyl)-2-propylcyclopentyl)pentyl)benzene (46).** (*Z*)-4,4-Bis(methoxymethyl)-

1,6-nonadiene was co-cyclised using method C and the zirconacycle elaborated using method E (allyl chloride) to give a mixture of **43** and **45** (0.324 g). The crude product was dissolved in CH_2Cl_2 (5 mL), 5% palladium on carbon (10 mg) added, and the mixture stirred under hydrogen (1.5 bar) for 48 h before filtration through celite, removal of solvent, and Kugelrohr distillation (210–220°C at 1 mmHg) gave the title compound **46** (0.308 g, 89%) as a colourless oil. ^{1}H NMR: δ 7.01–7.22 (5H, m), 3.255 (6H, s), 3.06–3.15 (4H, m,), 2.512 (2H, t, J=7.7 Hz), 1.685 (1H, d, J=13.2 Hz), 1.664 (1H, d, J=13.2 Hz), 1.40–1.60 (4H, m), 1.10–1.36 (8H, m), 0.83–0.98 (4H, m), 0.769 (3H, t, J=7.3 Hz) ppm. ^{13}C NMR: δ 143.05 (s), 128.54 (2d), 128.36 (2d), 125.70 (d), 78.02 (2t), 59.39 (2q), 45.35 (s), 45.34 (d), 45.13 (d), 39.55 (t), 39.49 (t), 36.63 (t), 36.13 (t), 34.22 (t), 31.69 (t), 29.86 (t), 28.36 (t), 21.61 (t), 14.67 (q) ppm. IR: 1454 (m), 1198 (m), 1111 (s), 1030 (w), 964 (m), 744 (m), 698 (m) cm^{-1}. LRMS (APCI): 347.3 ($M+H^+$, 57%), 315.4 ($M-MeOH+H^+$, 8), 283.2 ($M-2MeOH+H^+$, 100). Anal. Found: C, 79.51; H, 11.16. $C_{23}H_{38}O_2$ requires: C, 79.71; H, 11.05%.

(*E*)-6-Ethyl-1-phenyl-3-dodecen-1-ol (48). To a solution of zirconocene dichloride (0.585 g, 2 mmol) in THF (10 mL) under nitrogen at −78°C was added ethyl magnesium chloride (2.0 mL of a 2.0 M solution in THF, 4 mmol) followed by a solution of 1-octene (0.246 g, 2.2 mmol) in THF (1 mL). The reaction mixture was allowed to warm to 0°C over 2 h. At −78°C allyl chloride (0.30 mL, 3 mmol) was added followed by a solution of LiTMP (previously prepared by adding *n*-BuLi (1.9 mL of a 1.6 M solution in hexanes, 3 mmol) to a solution of tetramethylpiperidine (0.423 g, 3 mmol) in THF (4 mL) at 0°C and stirring for 20 min). The reaction was warmed to room temperature over 1 h, then cooled to −78°C and benzaldehyde (1.00 mL, 10 mmol) and $BF_3{\cdot}Et_2O$ (1.45 mL, 10 mmol) were added. After 15 min, the reaction was warmed to room temperature over 2 h. Methanol (2 mL) and saturated sodium bicarbonate solution (2 mL) were added and the mixture stirred for 1 h, then poured onto water (100 mL) and extracted with diethyl ether (3×50 mL). The combined extracts were washed with water (3×100 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed in vacuo. Purification by column chromatography (silica, 10% diethyl ether in *iso*-hexane) gave the title alcohol (0.513 g, 89%) as a pale yellow oil. ^{1}H NMR: δ 7.24–7.36 (5H, m), 5.32–5.61 (2H, m), 4.67 (1H, m), 2.35–2.54 (2H, m), 1.96–2.05 (2H, m), 1.16–1.39 (14H, m), 0.885 (3H, t, J=6.8 Hz), 0.842 (3H, t, J=6.6 Hz) ppm. ^{13}C NMR: δ 139.25 (s), 130.52 (d), 128.65 (d), 123.45 (2d), 122.49 (d), 120.99 (2d), 68.68 (d), 38.02 (t), 34.31 (d), 32.12 (t), 31.88 (t), 31.49 (t), 27.12 (t), 25.38 (t), 24.90 (t), 17.88 (t), 14.69 (q), 9.30 (q) ppm. IR: 3370 (m, broad), 1454 (m), 1048 (m), 970 (m), 757 (m), 699 (s) cm^{-1}. LRMS (CI, NH_3): 306 ($M+NH_4^+$, 8%), 288 (M^+, 100), 271 ($M-H_2O+H^+$, 37). HRMS (EI): Found: $M-PhCHOH+H^+$, 182.2024. $C_{13}H_{26}$ requires: 182.2035.

***rac*-(4*Z*)-2-Methyl-6-((2*S*,3*R*)-2,3,8,8-tetramethyl-7, 9-dioxaspiro[4.5]dec-2-yl)-4-hexen-2-yl acetate.** 2,2-Dimethyl-5-(2-methyl-prop-2-en-1-yl)-5-allyl-1,3-dioxane was co-cyclised using method C and the zirconacycle elaborated using method D (allyl chloride) but without protic work-up. The solvent was then removed in vacuo and benzene (8 mL) added. After filtration, acetone (2.5 mL) was added and the mixture heated at 85°C for 12 h in a sealed Carius tube. Removal of solvent and column chromatography (silica, 30–50% ether in petrol) yielded (4*Z*)-2-methyl-6-((2*S*,3*R*)-2,3,8,8-tetramethyl-7, 9-dioxaspiro[4.5]dec-2-yl)-4-hexen-2-ol **50** as an inseparable mixture of two diastereoisomers (ca. 4:1) (0.152 g, 49%). To isolate the major diastereoisomer in purer form the mixture of alcohols (0.113 g, 0.36 mmol) was acetylated [acetic anhydride (1 mL), pyridine (5 mL), DMAP (0.050 g), 5 h, room temperature]. Column chromatography (silica, 10% ether in petrol) gave the title acetate as a yellow oil (0.093 g, 73%) with partial separation of the diastereoisomers (9:1) ^{1}H NMR: δ 5.533 (1H, dtd, J=17.4, 6.3, 1.6 Hz), 5.476 (1H, dtd, J=17.4, 6.3, 1.6 Hz), 3.564 (4H, m), 2.470 (2H, d, J=6.0 Hz), 1.948 (3H, s), 1.944 (1H, dd, J=13.2, 6.4 Hz), 1.863 (2H, d, J=6.2 Hz), 1.719 (1H, ddq, J=11.4, 6.8, 6.7 Hz), 1.607 (1H, d, J=14.3 Hz), 1.406 (6H, s), 1.379 (3H, s), 1.371 (3H, s), 1.317 (1H, dd, J=13.3, 11.4 Hz), 1.032 (1H, d, J=14.2 Hz), 0.916 (3H, s), 0.883 (3H, d, J=6.9 Hz). ^{13}C NMR: δ 170.52 (s), 129.49 (d), 126.04 (d), 97.58 (s), 82.31 (s), 71.22 (t), 70.30 (t), 44.34 (t), 44.05 (d), 43.67 (s), 41.02 (t), 39.41 (s), 38.51 (t), 32.08 (t), 26.25 (q), 26.07 (q), 26.05 (q), 25.58 (q), 22.59 (q), 22.38 (q), 13.68 (q). IR: 1732 (s), 1658 (w), 1454 (m), 1382 (s), 1368 (s), 1252 (s), 1202 (s), 1156 (m), 1128 (m), 1071 (m), 1032 (m), 1014 (m), 831 (m) cm^{-1}. LRMS (CI, NH_3): 370 ($M+NH_4^+$, 14%), 353 ($M+H^+$, 19), 293 (98), 235 (100), 217 (73), 109 (32), 35 (58). HRMS (CI, NH_3): Found: $(M+H)^+$, 353.2682. $C_{21}H_{37}O_4$ requires: 353.2692.

***rac*-(1*R*,5*S*)- and *rac*-(1*R*,5*R*)-1-Methyl-bicyclo[3.3.0]octan-3-one-7-spiro-5′-(2′, 2′-dimethyl-1′, 3′-dioxane) 56 and 57.** 5-Allyl-2,2-dimethyl-5-(2-methyl-2-propenyl)-1, 3-dioxane (1 mmol) was co-cyclised using method C to afford zirconacycle **49** as a 4:1 isomeric mixture by NMR. The zirconacycle solution was cooled to −78°C and subjected to 3 evacuate-refill cycles with carbon monoxide gas. After stirring under a CO atmosphere (1.5 atm) for 1 h the reaction mixture was quenched at −70°C by the addition of methanol (3 mL), and then warmed to room temperature over 45 min. Water (25 mL) was added and the products extracted into ether (3×20 mL), dried ($MgSO_4$) and solvent removed. The residue was dissolved in dichloromethane (2 mL) and added in one portion to pyridinium dichromate (12.5 mmol) [made from CrO_3 (12.5 mmol, 1.25 g) and pyridine (25 mmol, 1.98 g)] in CH_2Cl_2 (30 mL). After stirring for 15 min, the dichloromethane solution was decanted from the black tarry deposit and the residue washed with ether (60 mL). The solvent was removed from the combined organic extracts in vacuo. The crude organic product was dissolved in ether (40 mL), filtered through Celite, washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and solvent removed in vacuo to yield a yellow oil. Column chromatography (silica, 20% ether in petrol) afforded a 9:2 mixture of the ketones **56** and **57** as a pale yellow oil (0.185 g, 62%). Further chromatography and recrystallisation (ether, 20 to −40°C followed by cold pentane wash) yielded the major (*cis*) diastereoisomer **56** in pure form (mp 75–77°C from ether, white needles), and the minor (*trans*) diastereoisomer **57** in 90% pure form (mp 68–70°C from ether, off white needles).

Major (*cis*) isomer **56**. ^{1}H NMR (360 MHz): δ 3.640 (1H, d, J=11.5 Hz), 3.614 (1H, d, J=6.9 Hz), 3.592 (1H, d, J=6.8 Hz), 3.569 (1H, d, J=11.7 Hz), 2.448 (1H, ddd, J=19.1, 7.9, 1.3 Hz), 2.321 (1H, dtd, J=10.5, 7.8, 2.2 Hz), 2.213–2.079 (3H, m), 2.111 (1H, dd, 19.3, 1.3 Hz), 1.678 (1H, d, J=14.5 Hz), 1.602 (1H, d, J=14.5 Hz), 1.377 (3H, s), 1.370 (3H, s), 1.301 (1H, dd, J=13.8, 9.8 Hz), 1.142 (3H, s). ^{13}C NMR: δ 219.44 (s), 97.85 (s), 70.88 (t), 69.60 (t), 52.24 (t), 46.71 (s), 46.62 (t), 46.30 (d), 43.19 (t), 42.64 (s), 40.36 (t), 28.05 (q), 24.76 (q), 23.08 (q). IR (CCl_4): 1742 (s), 1453 (m), 1406 (m), 1383 (m), 1253 (m), 1201 (m) cm^{-1}. Anal. Found: C, 70.30; H, 9.44. $C_{14}H_{22}O_3$ requires: C, 70.56; H, 9.30%. Minor (*trans*) isomer 57. ^{1}H NMR (360 MHz): δ 3.838 (1H, dd, J=11.3, 0.7 Hz), 3.773 (1H, dd, J=11.3, 1.5 Hz), 3.650 (1H, dt, J=11.3, 0.8 Hz), 3.574 (1H, dd, 11.3, 1.5 Hz), 2.223 (1H, dd, J=17.0, 6.8 Hz), 2.202 (1H, d, J=16.5 Hz), 2.120–1.900 (4H, m), 1.623 (1H, d, J=13.0 Hz), 1.438 (3H, s), 1.422 (3H, s), 1.427 (1H, m), 1.223 (1H, dq, J=13.0, 0.8 Hz), 0.824 (3H, s). ^{13}C NMR: δ 220.09 (s), 97.72 (s), 70.57 (t), 69.87 (t), 53.47 (t), 48.41 (d), 46.91 (s), 44.66 (s), 43.05 (t), 38.53 (t), 32.25 (t), 25.56 (q), 22.07 (q), 19.84 (q). IR (CCl_4): 1747 (s), 1451 (w), 1382 (m), 1202 (s), 1095 (s), 832 (m) cm^{-1}. LRMS (CI): 256 ($M+NH_4^+$, 44%), 239 ($M+H^+$, 100), 223 (25), 181 (11), 163 (14). HRMS (CI, NH_3): Found: $(M+NH_4)^+$, 256.1902. $C_{14}H_{26}O_3N$ requires: 256.1913.

***rac*-(3*R*,4*S*)-1-Benzyl-3,4-dimethyl-3-(3-methyl-2-butenyl)-pyrrolidine (52).** *N*-Allyl-*N*-benzyl-*N*-(2-methylallyl)-amine[19] (0.201 g, 1 mmol) was co-cyclised using method C, and the zirconacycle elaborated using method D (methallyl chloride). Column chromatography (silica, 10–50% diethyl ether in petrol) gave the title compound containing an equimolar amount of 1-benzyl-3,3,4-trimethyl-pyrrolidine (0.185 g). Spectral data is given for the title compound only: ^{1}H NMR: δ 7.26–7.38 (5H, m), 5.165 (1H, t, J=6.7 Hz), 3.710 (1H, d, J=13.2 Hz), 3.616 (1H, d, J=13.2 Hz), 2.937 (1H, dd, J=14.2, 7.4 Hz), 2.480 (2H, broad s), 2.304 (1H, dd, J=14.2, 7.4 Hz), 2.102 (1H, dd, J=14.2, 7.4 Hz), 2.00 (1H, m), 1.877 (1H, dd, J=14.3, 7.4 Hz), 1.737 (3H, s), 1.658 (3H, s), 1.024 (3H, s), 0.937 (3H, d, J=7.0 Hz) ppm. ^{13}C NMR: δ 139.71 (s), 133.12 (s), 128.78 (2d), 128.27 (2d), 126.89 (d), 121.68 (d), 65.43 (t), 61.43 (t), 61.00 (t), 43.49 (d), 43.28 (s), 33.51 (t), 26.25 (q), 25.50 (q), 18.15 (q), 13.22 (q) ppm. IR: 1494 (s), 1453 (s), 1375 (s), 1124 (m), 1072 (m), 1028 (m) cm^{-1}. LRMS (ES): 258 ($M+H^+$, 100%). HRMS (EI): Found: M^+, 257.2123. $C_{18}H_{27}N$ requires: 257.2144.

***rac*-(*E*)-5-[(1*S*,2*R*)-1-(Methoxymethyl)-2-methylcyclopentyl]-1-phenyl-3-penten-1-ol (54).** 2-Methoxymethyl-1,6-heptadiene (0.196 g, 1 mmol) was co-cyclised using method C, and the zirconacycle elaborated using method E (allyl chloride) to afford, after chromatography (silica, 10–25% diethyl ether in petrol) the title compound (0.078 g, 27%) as a pale yellow oil. ^{1}H NMR: δ 7.24–7.37 (5H, m,), 5.602 (1H, dt, J=15.1, 7.4 Hz), 5.406 (1H, dt, J=15.1, 7.4 Hz), 4.609 (1H, dd, J=5.2, 7.6 Hz), 3.298 (3H, s), 3.152 (1H, d, J=8.8 Hz), 3.101 (1H, d, J=8.8 Hz), 2.38–2.56 (3H, m), 2.098 (1H, dd, J=7.4, 13.8 Hz,), 1.887 (1H, dd, J=7.4, 13.8 Hz), 1.77–1.85 (2H, m), 1.20–1.64 (5H, m), 0.906 (3H, d, J=6.6 Hz) ppm. ^{13}C NMR: δ 144.18 (s), 132.69 (d), 128.48 (2d), 127.52 (d), 127.48 (d), 126.00 (2d), 79.40 (t), 73.50 (d), 59.41 (q), 47.67 (s), 43.04 (t), 40.53 (d), 35.01 (t), 33.59 (t), 33.26 (t), 22.06 (t), 15.36 (q) ppm. IR: 3414 (s broad), 1603 (w), 1493 (m), 1454 (s), 1195 (m), 1107 (s), 972 (s), 700 (s) cm^{-1}. LRMS (APCI): 271.2 ($M-H_2O+H^+$, 32%), 239.1 ($M-H_2O-MeOH+H^+$, 100). HRMS (EI): Found: $(M-H_2O)^+$, 270.1981. $C_{19}H_{26}O$ requires: 270.1984.

***rac*-(1*S*,2*R*)-1-(Methoxymethyl)-2-methyl-1-(3-methyl-2-butenyl) cyclopentane (55).** 2-Methoxymethyl-1,6-heptadiene (0.196 g, 1 mmol) was co-cyclised using method C, and the zirconacycle elaborated using method D (methallyl chloride) to afford, after chromatography (silica, 5–10% diethyl ether in petrol) and Kugelrohr distillation (100–105°C at 0.8 mmHg) the title compound (0.070 g, 36%). ^{1}H NMR: δ 5.141 (1H, t septet, J=7.4, 1.0 Hz), 3.294 (3H, s), 3.161 (1H, d, J=8.8 Hz), 3.075 (1H, d, J=8.8 Hz), 2.025 (1H, dd, J=14.3, 7.4 Hz), 1.76–1.95 (3H, m), 1.716 (3H, d, J=1.0 Hz), 1.617 (3H, d, J=1.0 Hz), 1.22–1.58 (5H, m), 0.924 (3H, d, J=6.8 Hz) ppm. ^{13}C NMR: δ 132.76 (s), 121.72 (d), 78.76 (t), 59.29 (q), 48.04 (s), 40.49 (d), 33.81 (t), 33.07 (t), 29.51 (t), 26.29 (q), 22.31 (t), 17.91 (q), 15.34 (q) ppm. IR: 1451 (s), 1375 (s), 1259 (m), 1198 (m), 1110 (s), 964 (m) cm^{-1}. LRMS (APCI): 197.1 ($M+H^+$, 100%), 165.2 ($M-MeOH+H^+$, 10). Anal. Found: C, 79.48; H, 12.38. $C_{13}H_{24}O$ requires: C, 79.53; H, 12.32%.

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