# *In*/*Out* Isomerism

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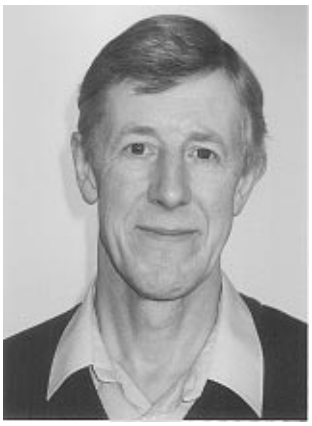
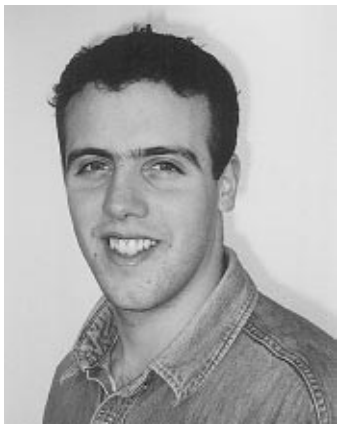
## Contents





Roger Alder was born near Stow-on-the-Wold, in 1937. He was educated at Oxford University, where he obtained a D.Phil. with Mark Whiting in 1962. After postdoctoral work with James B. Hendrickson at UCLA and Brandeis University, he moved to Bristol University in 1965, where he is now Professor of Organic Chemistry. He has worked on the unique chemistry of medium-ring bicyclic compounds, strong amine bases, such as 1,8-bis(dimethylamino)naphthalene, powerful methylating agents, the azulene/naphthalene rearrangement, and the conformational effects of quaternary centers. He was awarded the Bader Prize of the Royal Society of Chemistry in 1993. His current research interests include examining the potential of stable carbenes as bases and nucleophilic catalysts, and the preparation of polymers with novel structures controlled by quaternary centres.



Stephen East was born in Surrey, England, in 1970. He studied chemistry at the University of Bristol and received his B.Sc. Honours degree in 1992. He has just completed his Ph.D. under the supervision of Roger Alder in the area of medium-ring bicyclic amines, particularly focusing on synthetic routes toward 1-aza- and 1,7-diaza-bicyclo[5.5.5]heptadecane.

## I. Introduction

Bridged bicyclic structures containing small or common-sized rings adopt structures in which the bridgehead substituents point outward; representative examples are bicyclo[1.1.1]pentane (**1**) and camphor (**2**). For many years this was the only known situation, but other geometries become possible in compounds containing medium (7- to 12-membered) and large rings.

The first compounds in which these other possibilities were realized were the macrocyclic diammonium ions prepared by Simmons and Park in 1968 (Figure 1).[1−3] and it was they who introduced the term *in*/*out* stereoisomerism and called the process of conformational interconversion of these isomers homeomorphic isomerism (Figure 2).[4] Shortly after this, Lehn reported the first cryptands which utilized inside lone pairs on bridgehead nitrogen atoms in the complexation of metal ions,[5−12] and interest in compounds which exhibit this isomerism has continued to grow strongly ever since.

The first compounds with *in*-CH bridgeheads were reported simultaneously by Gassman and Thummel,[13,14] and by Park and Simmons.[15] Gassman and Thummel used a Diels−Alder approach, reacting *cis*,*trans*-1,3-cyclodecadiene (**3**) with the powerful dienophile hexafluoro-2-butyne to form **4**, along with a $2\pi + 2\pi$ product. Park and Simmons used the acyloin reaction of *cis*- and *trans*-isomers of **5** to obtain *in*,*out*- and *in*,*in*-bicyclo[8.8.8]hexacosane (**6**).

It was soon realized that inside C−H groups or lone pairs on bridgehead nitrogen atoms were possible in surprisingly small ring systems. The properties of 1-azabicyclo[3.3.3]undecane (manxine, **7**) indicated that it contained an almost flat nitrogen atom,[16−18] and suggested that in only slightly larger ring systems the nitrogen would invert to place the lone pair inside. This is indeed the case with *out*-6*H*-1-azabicyclo[4.4.4]tetradecane (**8**) which only forms an outside protonated ion with great reluctance.[19] The

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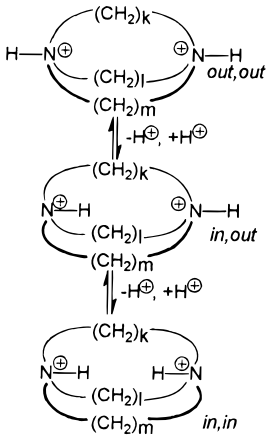



**Figure 1.** Macrocyclic diamines prepared by Simmons and Park[1–3] (*k*, *l*, and *m* were in the range of 6−10), showing equilibration via protonation−deprotonation reactions.

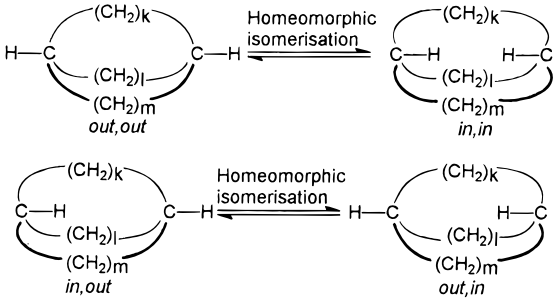
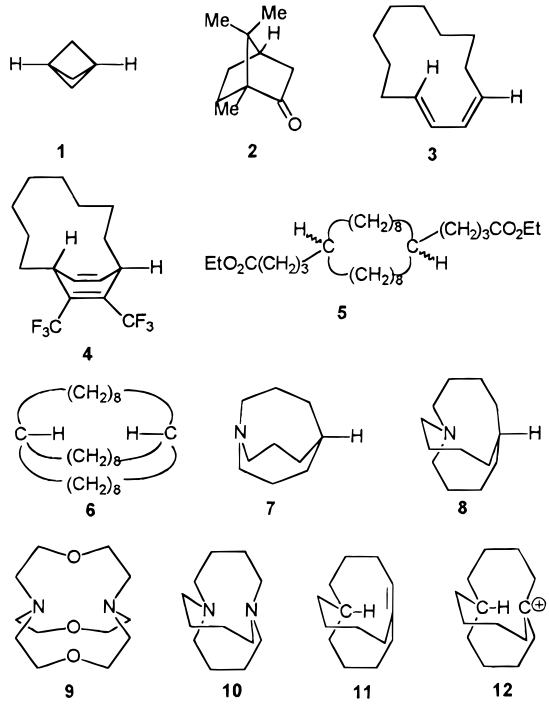



**Figure 2.** Homeomorphic isomerization[2] of *out,out*- to *in,in*- and *in,out*- to *out,in*-isomers.

smallest cryptand, **9**, has both its lone pairs inside and forms a *in,in*-diprotonated dication;[20,21] larger analogues such as [2.2.2]cryptand also have inside lone pairs.[22] Thus the borderlines where *in,out*- and *in,in*-isomers become possible must lie within the region of medium-ring bicyclic compounds. In these compounds, *in,out*- and *in,in*-isomers are by no means strain-free, and there will often be severe nonbonded interactions involving an inside hydrogen or lone pair, but an important point is that the alternative *out,out*-isomer is itself usually severely strained, due to nonbonding interactions between methylene groups in the bridges.

In these medium-ring compounds any process which allows the bridgehead atoms to move toward each other leads to a reduction of strain. Interactions between the bridgehead atoms in these compounds often give rise to unusual chemistry as a result of this effect.[23–25] Thus 1,6-diazabicyclo[4.4.4]tetradecane (**10**), which has both its lone pairs inside, is very readily oxidized to a stable radical cation and can be converted to both *in*- and *out*-monoprotonated ions,[26,27] and *in*-bicyclo[4.4.4]tetradec-1-ene (**11**) is very easily converted to the $\mu$-hydrido cation **12**.[28,29]

This review covers the basic phenomenon of *in/out* isomerism, nomenclature, the question of the range of stability of the various isomers, mechanisms for their interconversion, the accessibility and special reactivity of inside functionality, and the (relatively few) natural products which show this isomerism. The field of cryptand chemistry has been thoroughly reviewed,[8–12] so only aspects which are particularly relevant to *in/out* isomerism are covered here.




## *II. Nomenclature*

The *in/out* nomenclature for bridged bicyclic ring systems was introduced by Simmons and Park[1–3] and is simple and graphic. Unfortunately this nomenclature is not unambiguous or consistent, as has been noted by several authors, since both configuration and conformation are involved.[30] An *out,out-/in,in*-isomer pair are in principle different conformers of the same configuration, whereas an *out,out-/in,out*-isomer pair are genuinely different configurations. An *out,out-/in,out*-isomer pair of bridged bicyclic compounds is related to a *cis-/trans*-isomer pair of fused bicyclo[*k*.l.0]alkanes. This relationship is particularly clear for bicyclo[*k*.l.1]alkanes where the *in*-substituent is often not significantly "inside" the molecule in the same way as it is in a compound where all the bridges are the same (bicyclo[*k*.*k*.*k*]-alkane) or of closely similar lengths; this point is discussed further in section V of this review.

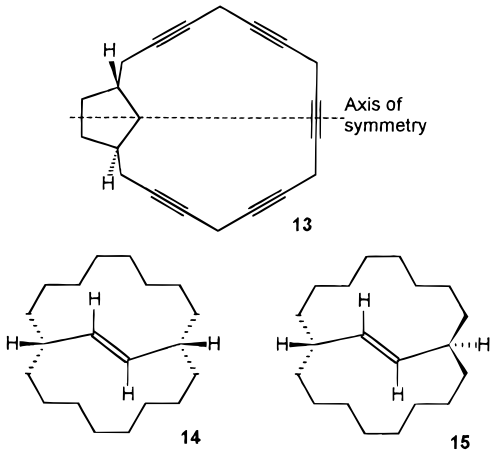
### A. Configuration

The question of configuration is readily settled. In the general bicyclo[*k*.*l*.*m*]alkane ($k \neq l \neq m$), four configurations: *(R,R)*, *(R,S)*, *(S,R)*, and *(S,S)* may exist. The *(R,R)*- and *(S,S)*-isomers may exist in *in,out* or *out,in* conformations, while the *(R,S)*- and *(S,R)*-isomers will be either *in,in* or *out,out*. It is worth noting that the *R/S* nomenclature, in its extended form,[31] is not limited to cases where $k \neq l \neq m$, but can handle all possibilities. When two of the bridges are the same, the *r/s* system is used, and this also works if all the bridges are the same.[32] Thus the stable conformation of *out*-6H-1-azabicyclo[4.4.4]-tetradecane (**8**) with the lone pair inside[19] is the 1*s*,6*s*-isomer.

### B. Conformation

The conformational situation is relatively clear cut until some of the bridges become really large. *In/*

*out* isomerism is then likely to lose its simple meaning, since there will usually be large numbers of low-energy conformations, whole families which might be called *in,in* or *out,out*, and where *out,out/in,in* and *in,out/out,in* interconversions will be ill-defined and hard to separate from other conformational processes. It is not difficult to think of compounds which are formally *(R,R)* or *(S,S)* and thus belong to the *in,out* family, but where these terms lose their meaning. For example *(S,S)*-bicyclo[16.2.1]heneicosa-3,6,9,12,15-pentayne (**13**) can adopt a low-energy conformation where the two bridgehead hydrogens are identical by symmetry! The compounds **14** and **15** have been obtained as two components of an inseparable mixture of stereoisomers of bicyclo[8.8.2]icos-19-ene. Molecular mechanics calculations suggested that the preferred conformation of **14** is one where the double bond and the bridgehead hydrogens lie more or less perpendicular to the plane of the 20-membered ring, so that **14** "does not exist in homeomorphic forms".[33] It appears to the reviewers that **15** could easily adopt a related conformation with $C_2$ symmetry in which the two bridgehead hydrogens would be identical like **13**.




Other problems arise when some of the rings become really large. As Haines and Karntiang[34] have pointed out, an *in,out*-bicyclic compound (A) (Figure 3) can assume, at least in theory, an *out,out* conformation of the type (B), and also *in,in* conformations. The normal assumption made is that the chains are not intertwined; this is likely to be true until quite large rings are involved (greater than 20 atoms).

There are therefore obvious difficulties in enshrining the concept of *in,out* isomerism in strict rules of nomenclature. Yet the idea is a simple and graphic one which has proved its worth, and it seems to the present reviewers that it is more appropriate to use *in/out* as a useful description of conformation like "chair" or "twist". Much of the interest in this area

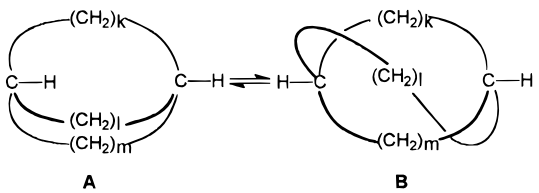
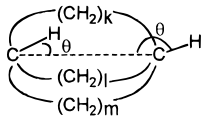



**Figure 3.** An *in,out*-bicyclic compound (A) at equilibrium with an intertwined *out,out* conformation (B).[34]




in-CH $\theta \geq 0°$
out-CH $\theta \leq 180°$

**Figure 4.** The angle $\theta$ between the substituent, the bridgehead atom to which it is attached, and the other bridgehead atom can determine the accessibility of a bridgehead substituent.

lies in the unusual properties of functionality hidden inside the ring system and this often depends on the degree of "in-ness" and "out-ness" of the bridgehead substituent. This is usefully, if only approximately, measured by the angle $\theta$ between the substituent, the bridgehead atom to which it is attached, and the other bridgehead atom (Figure 4).[34] This is discussed in section V of this review.

## III. Stabilities of *Out,out-*/*In,out-*/*In,in*-Isomers as a Function of Bridge Length

*Out,out*-isomers are strongly preferred for smaller bicyclic systems, in particular for those built from small (3- and 4-membered) and common-sized (5- and 6-membered) rings. The borderlines for existence of the *in,out*- and *in,in*-isomers are by no means obvious. Clearly these will depend strongly on the bridgehead substituents, but the only cases which have been examined in any depth are bridgehead H−C and H−$N^+$ groups and lone pairs on bridgehead nitrogen atoms. It is broadly clear that for these cases *in,out*- and *in,in*-isomers do become observable for bicyclic compounds built from medium rings, but there is still limited experimental evidence to accurately define these borderlines. While the *out,out*-, *in,out*-, and *in,in*-isomers will be separated by high barriers for compounds with carbon bridgeheads, the situation is quite different for bridgehead amines where nitrogen inversion leads to equilibration of the isomers so that thermodynamic preference can easily be discovered. Since the barriers protecting unstable structures are likely to be quite high for hydrocarbons, highly strained isomers like *in,out*-bicyclo[3.3.1]-nonane may well be isolable if suitable preparative methods can be devised. Compounds where a bridgehead hydrogen atom is enolizable represent another interesting case: how easily can such isomers be interconverted?

### A. Hydrocarbons

The question of relative thermodynamic stability of the *out,out*-, *in,out*-, and *in,in*-isomers of bicyclic hydrocarbons is amenable to molecular mechanics calculations. However, bicyclic hydrocarbons with large enough bridges to permit *in,out*- and *in,in*-isomers are conformationally very complex, and it was not until the advent of multiple minimum search procedures[35] that this problem could be tackled realistically. In an early application of stochastic search procedures, Saunders performed calculations for 32 bicyclic hydrocarbons ranging from bicyclo-[3.2.2]nonane to bicyclo[6.6.6]eicosane, located all the conformations of each isomer, and was thus able

**Table 1. MM2 Calculated Steric Energies of Lowest Energy Conformations of Bicyclic Hydrocarbons (in kcal/mol)[a]**

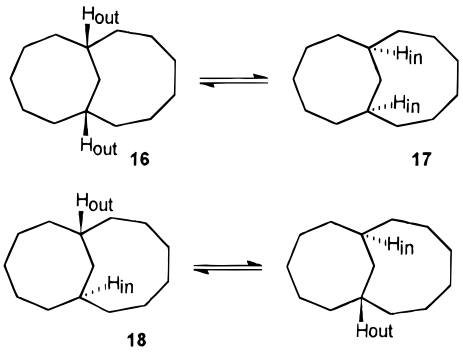
| bicyclic hydrocarbon | *out,out* | in,out | in,in |
|---|---|---|---|
| bicyclo[3.2.2]nonane | 24.25 | 81.43 | |
| bicyclo[3.3.1]nonane | 18.26 | 64.43 | |
| bicyclo[4.2.1]nonane | 24.36 | 68.04 | |
| bicyclo[5.1.1]nonane | 46.75 | 87.44 | |
| bicyclo[3.3.2]decane | 29.95 | 66.78 | 130.17 |
| bicyclo[4.2.2]decane | 29.60 | 67.14 | |
| bicyclo[5.2.1]decane | 30.10 | 50.90 | |
| bicyclo[4.3.1]decane | 24.20 | 48.30 | |
| bicyclo[3.3.3]undecane | 37.28 | 70.17[b] | 119.57 |
| bicyclo[4.3.2]undecane | 37.26 | 56.15 | 107.83 |
| bicyclo[5.2.2]undecane | 38.22 | 53.96 | |
| bicyclo[4.4.1]undecane | 27.19 | 37.52 | 62.23 |
| bicyclo[5.3.1]undecane | 26.19 | 37.52 | 63.93 |
| bicyclo[4.3.3]dodecane | 48.60 | 55.80 | 93.45 |
| bicyclo[4.4.2]dodecane | 44.09 | 51.43 | 84.68 |
| bicyclo[5.3.2]dodecane | 43.75 | 48.47 | 86.46 |
| bicyclo[5.4.1]dodecane | 32.98 | 33.99 | 48.02 |
| bicyclo[6.3.1]dodecane[c] | 43.43 | 50.53 | |
| bicyclo[4.4.3]tridecane | 58.35 | 54.81 | 82.43 |
| bicyclo[5.3.3]tridecane | 56.46 | 52.43 | 78.20 |
| bicyclo[5.4.2]tridecane | 48.00 | 46.51 | 67.33 |
| bicyclo[5.5.1]tridecane | 36.55 | 37.45 | 41.55 |
| bicyclo[7.3.1]tridecane[c] | 32.50 | 31.34 | |
| bicyclo[4.4.4]tetradecane | 68.66 | 56.45 | 71.92 |
| bicyclo[5.4.3]tetradecane | 63.21 | 53.01 | 69.21 |
| bicyclo[5.5.2]tetradecane | 53.43 | 48.84 | 55.97 |
| bicyclo[6.5.1]tetradecane | 42.16 | 40.18 | 42.44 |
| bicyclo[5.4.4]pentadecane | 64.86 | 55.03 | 63.61 |
| bicyclo[6.6.1]pentadecane | 48.36 | 44.06 | 46.35 |
| bicyclo[7.5.1]pentadecane | 41.83 | 41.78 | 41.48 |
| bicyclo[5.5.4]hexadecane | 63.79 | 54.77 | 57.08 |
| bicyclo[5.5.5]heptadecane | 60.83 | 54.16 | 49.78 |
| bicyclo[6.5.5]octadecane | 57.88 | 50.81 | 45.61 |
| bicyclo[6.6.6]eicosane | 47.42 | 43.62 | 36.4 |

[a] All data is taken from reference 36 unless otherwise stated. [b] Calculation by present authors. [c] Data from ref 77.

predict the thermodynamic preferences.[36] His results are summarized in Table 1. According to these calculations, the *in,out*-isomers become the most stable for several bicyclotridecanes ([4.4.3], [5.3.3], and [5.4.2]), and the *in,in*-isomer is most stable for bicyclo[5.5.5]heptadecane.

Unfortunately, there is little experimental data to test these predictions. Saunders and Krause[37] prepared all three isomers of bicyclo[6.5.1]tetradecane **16**−**18** and found an *out,out*/*in,in* equilibrium ratio of 4 at 50 °C in toluene, in satisfactory agreement with the prediction of very similar strain energies for these isomers. Equilibration with the *in,out*-isomer **18** (calculated to be most stable) was not established. The only other case where thermodynamic equilibria have been established for C−H bridgeheads concerns a pair of macrobicyclic *in,out*-/*out,in*-isomers (see section IV).

What is clear is that it is possible to prepare examples of *in,out*-compounds which are undoubtedly unstable with respect to their *out,out*-isomers. Thus Winkler and co-workers[38] achieved the synthesis of *in,out*-bicyclo[5.3.1]undecan-11-one (**19**) by means of



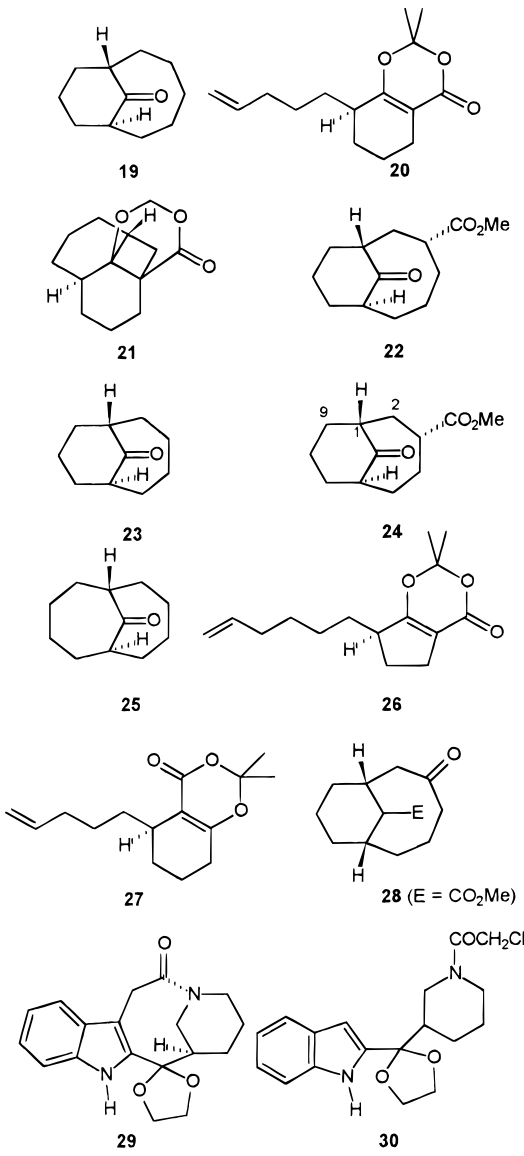

the intramolecular photocycloaddition of **20** to give **21**, acid-catalyzed ring opening of this to **22**, hydrolysis, and Barton decarboxylation. Formation of *trans*-isomer **19** was explained as arising from a chairlike transition state for the photoaddition. All attempts to effect equilibration with the known *out,out*-isomer[39] of **19** were unsuccessful, even though the bridgehead hydrogens are, in principle, enolizable and the *out,out*-isomer is estimated to be 10 kcal/mol more stable. It was suggested that the bridgehead hydrogens probably lie nearly parallel to the carbonyl group so that their kinetic acidity will be low. Equilibration was also unsuccessful in the bicyclo-[6.3.1]dodecane series, but could be effected in the corresponding [7.3.1] and [9.3.1] compounds.[40] In these larger rings, bridgehead enolate formation is relatively easy.

The even more strained *in,out*-bicyclo[4.3.1]decan-10-one **23** was prepared by a similar sequence of reactions,[41] but in this case both diastereoisomers were obtained in the photocycloaddition in a 1:5 ratio, with the *out,out*-isomer predominating. The strain energy difference between *in,out*- and *out,out*-isomers is calculated to be 20 kcal/mol in this case. The high strain in the *in,out* series is illustrated by a C2−C1−C9 angle of 130° in **24**.

Winkler and co-workers have prepared *in,out*-bicyclo[4.4.1]undecan-11-one (**25**) by similar methodology[42] and also used this to prepare the tricyclic nucleus of the ingenane diterpenes (see section VII). In this instance the intramolecular photocycloaddition of **26** occurred to both faces of the dioxenone double bond so that two diastereomeric photoadducts were obtained which both gave **25** after acid-catalyzed fragmentation, hydrolysis, and decarboxylation. Winkler *et al.*[43] have found that transposition of the chromophore has a dramatic effect on the stereochemical outcome of the intramolecular dioxenone photocycloaddition reaction, so that photolysis of **27** leads to the *out,out*-isomer **28** after hydrolysis. They have proposed that the determining factor is that the first bond formation always occurs from the oxygen-substituted dioxenone carbon.[44]

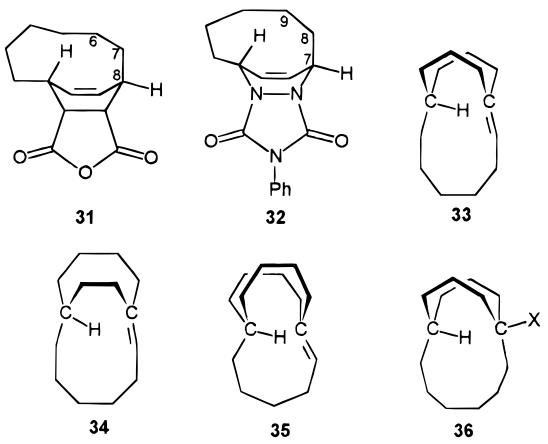
Sundberg and Smith obtained both *in*- (**29**) and *out*-CH isomers of a complex [5.3.1] system containing an indole by photocyclization of **30**.[45] After hydrolysis of the dioxolane, the *in*-isomer of the corresponding ketone could be converted to the *out*-isomer through the enolate. It is not obvious why equilibration can be achieved in this instance, and not for **19**.

Gassman and co-workers prepared a series of derivatives of *in,out*-bicyclo[*n*.2.2]alkanes ($n = 5-8$)



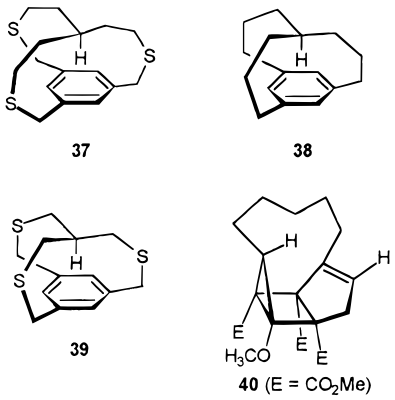

through Diels−Alder reactions of *cis,trans*-1,3-cycloalkadienes.[13,14,46−50] Few molecular mechanics calculations on these systems have been reported,[51] and the *in,out*-isomers may be thermodynamically preferred for the larger systems, but it is plain that the *in,out*-isomers with $n = 5$ or 6 are severely strained. This is shown by some extremely large C−C−C angles in these compounds. Thus C6−C7−C8 is 123.9° in **31**,[48] and C7−C8−C9 is 122.6° in **32**.[50] Compound **32** isomerized to the corresponding *out,out*-isomer when heated in various solvents to 50−65 °C, and on the basis of trapping experiments, it was proposed that the mechanism of this reaction involved heterolytic cleavage of the C−N bond adjacent to the *in* bridgehead.

In many respects, the most interesting cases are those where all the bridges are of similar length, and especially the symmetrical [3.3.3], [4.4.4], and [5.5.5] hydrocarbons. Bicyclo[3.3.3]undecane (manxane)[52] certainly prefers an *out,out* structure, and all known derivatives are *out,out*.[16,17,53] However there is only limited experimental evidence concerning derivatives of bicyclo[4.4.4]tetradecane and bicyclo[5.5.5]heptadecane is unknown. Saunders' calculations (Table 1) predict the *in,out*-isomer is the most stable for the former and the *in,in*-isomer for the latter, but clearly suggest that all isomers should be isolable. McMurry and Hodge[28] prepared *in*-bicyclo[4.4.4]tetradec-1-ene (**11**) in 30% yield by titanium(0) cyclization of 6-(4-oxobutyl)cyclodecanone and were able to hydrogenate this slowly to *in,out*-bicyclo[4.4.4]tetradecane (the former is a hyperstable[54] alkene). A small amount of an isomer of **11** (presumably the *out*-isomer which is calculated to be 7.4 kcal/mol less stable) was obtained in the cyclization reaction, but no further work on this has been reported. Other attempts to prepare *out*-bicyclo[4.4.4]tetradec-1-ene and bicyclo-[4.4.4]tetradecadiene derivatives led to unexpected rearrangements and cyclizations, presumably due to the high strain in these systems.[55,56] McMurry and Lectka[57] subsequently prepared bicyclo[6.3.3]-1-tetradecene (**33**), bicyclo[6.4.2]-1-tetradecene (**34**), and bicyclo[5.4.4]-1-pentadecene (**35**) by similar routes involving Ti(0) couplings. In all cases, the *in*-isomers were obtained, and **33** was converted to the *in,out* saturated hydrocarbon **36** (X = H) by hydrogenation. Addition of HCl to **33** gave *out*-1-chloro-*in*-8*H*-bicyclo-[6.3.3]tetradecane (**36**, X = Cl). In all these cases, it seems likely that the thermodynamically most stable isomers have been obtained. The remarkable chemistry associated with the bridgehead alkenes is discussed in section VI.




Pascal and Grossman[58] recognized that the previously reported[59] 2,8,17-trithia[4[5,12]][9]metacyclophane (**37**) was the inside isomer; the methine proton was found at $\delta$ −1.68 ppm. Pascal and co-workers[60] then used this compound to prepare *in*-[3[4,10]][7]metacyclophane (**38**) which showed a methine resonance at $\delta$ −4.03. A crystal structure of this compound could not be obtained, but molecular mechanics calculations suggest that the methine proton would be only 1.78 Å above the aromatic ring. A series of trithiametacyclophanes were prepared and the structures of some of these compounds determined.[61] In the smallest cyclophane **39**, the methine hydrogen was found to be only 1.69 Å above the aromatic ring, significantly shorter than calculated by MM2 and MNDO.

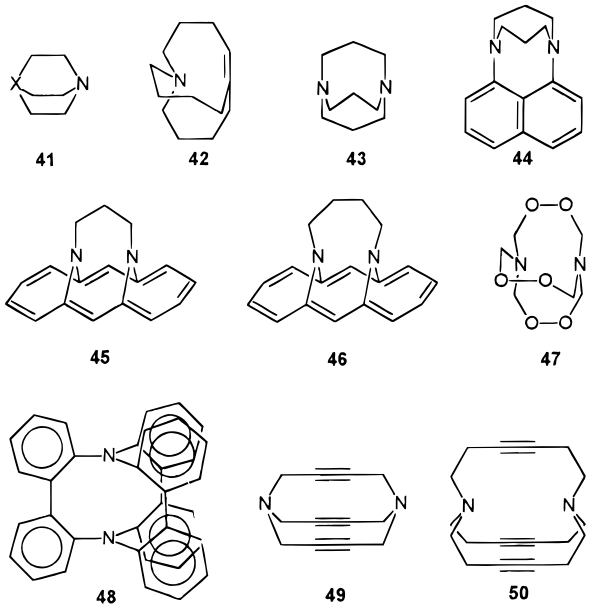
Tochtermann *et al.*[62] have reported the synthesis of the bridged bicyclo[2.1.0]pentane derivative **40**, with inside configuration. This can be considered as a [5.4.2] ring system with extra bridges.




## B. Amines

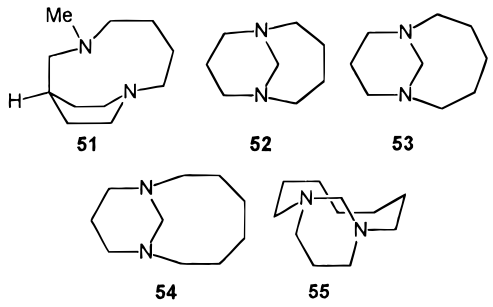
The *out*- and *in*-isomers of bridgehead amines and diamines are equilibrated by nitrogen inversion so that the thermodynamic preference can readily be discovered. The symmetric monoamines: 1-azabicyclo-[2.2.2]octane (quinuclidine) (**41**, X = CH), 1-azabicyclo-[3.3.3]undecane[16,17] (manxine, **7**), and *out*-6H-1-azabicyclo[4.4.4]tetradecane[19] (**8**) form a series in which the nitrogen atoms appears to be successively pyramidal *out*, essentially flat, and pyramidal *in*. Structural data on **7** and **8** have not be obtained, but an *in,out* conformation is preferred by the outside-protonated ion of 1,6-diazabicyclo[4.4.4]tetradecane,[63] a compound which should be structurally very similar to **8**. The isomer of **8**, *in*-6*H*-1-azabicyclo[4.4.4]-tetradecane is predicted by calculations to also exist with its lone pair inside, as of course are both isomers of 1-azabicyclo[5.5.5]heptadecane, but these compounds have evaded all attempts at synthesis so far. 1-Azabicyclo[4.4.4]tetradec-5-ene (**42**) also appears to exist with its nitrogen lone pair inside.[64] The photoelectron spectrum of **42** indicates a strong lone pair/$\pi$-bond interaction, and the compound reacts rapidly with acid to form a propellane.

In the diamine series, 1,4-diazabicyclo[2.2.2]octane (DABCO, **41**, X = N) is *out,out*; 1,5-diazabicyclo[3.3.3]-undecane (**43**) probably has nearly flat nitrogen atoms to judge from its photoelectron spectrum; and 1,6-diazabicyclo[4.4.4]tetradecane (**10**) adopts an *in,-in* structure.[65] The naphtho-1,5-diazabicyclo[3.3.3]-undecane (**44**) was found by X-ray structure determination[66] to have practically flat nitrogen atoms, the C−N−C angles averaging 118.6°. The bridged annulene **45** which also contains a [3.3.3] ring system, also had almost flat nitrogen atoms,[67] the sum of the angles at nitrogen being 357.4°. In the annulene **46** with a $(CH_2)_4$ bridge, a [4.3.3] system, the sum of the C−N−C angles was 357.6°.[68] While the parent 1,6-diazabicyclo[4.4.4]tetradecane (**10**) adopts an *in,in* geometry, hexamethylene triperoxide diamine **47**, a compound first prepared in 1885,[69] shows completely flat nitrogen atoms.[70] This is probably due to delocalization of the nitrogen lone pair electrons into the C−O bonds (a manifestation of the anomeric effect). The hexabenzo derivative of 1,6-diazabicyclo[4.4.4]-tetradecane (**48**, described as a triphenylamine double-decker) has been prepared.[71] From the shielding of the aromatic protons in the $^1$H NMR spectrum, it was suggested that the nitrogen atoms were more or less flat (as is generally found for triphenylamines) and about 2.5 Å apart. Gleiter and co-workers[72,73] have recently reported the preparation of the triynes **49** and **50**, describing these as novel $\pi$-boat cage compounds. The [4.4.4] derivative is unstable, and its reactions have not been studied, but the [6.6.6] compound could be hydrogenated with Lindlar's catalyst to the *cis,cis,cis*-triene. The conformation of the nitrogen atoms in these compounds is unknown, but **49** is probably like a "stretched" DABCO **41**, X = N, with outside lone pairs, while **50** should resemble a stretched **10**, and have its lone pairs inside. Finally, in studying the photoelectron spectra of the series of medium-ring bicyclic diamines [3.3.3], [4.3.3], [4.4.3], [4.4.4], it was found that the *average* lone pair ionization energy reached a minimum at 1,6-diazabicyclo[4.4.3]tridecane.[74,75] This average probably mainly reflects the p character of the nitrogen lone pair, and thus the degree of flattening of the nitrogen atoms.




It therefore seems that in these medium-ring amines and diamines, where the bridges are all of similar length, the transition from an *out,out* to *in,in* structure takes place via amines with almost flat nitrogen atoms. This does not seem to be the case where the constituent bridges in the bicyclic structure are of notably different length. Thus Nelsen and Gannett found that 6-methyl-1,6-diazabicyclo[6.2.2]-dodecane (**51**) could be clearly described as an *in,out* 6-atom-bridged boat piperidine.[76] A thorough study of a series of [*n*.3.1]diamines[77] also points to the transition from *out* to *in* taking place through well-defined *in,out*-isomers. In this series, all the compounds have lowest energy conformations with chair-form six-membered hexahydropyrimidine rings, so that *out,out*-isomers correspond to an axial,axial (ax,ax) fusion of the remaining bridge, *in,out* to axial,equatorial, (ax,eq) and *in,in* to (eq,eq). Although X-ray structural data could not be obtained, $^1$H NMR coupling constants provided good evidence of the solution conformations, while the question of *out,out* vs *in,out* in the gas phase could be deduced from the photoelectron spectra. It was found that 1,6-diazabicyclo[4.3.1]decane (**52**) was *out,out* in both

gas phase and in $CDCl_3$ solution, 1,7-diazabicyclo-[5.3.1]undecane (**53**) was about 10−15% *in,out* in the gas phase, but still entirely *out,out* in solution, 1,8-diazabicyclo[6.3.1]dodecane (**54**) was entirely *in,out* in the gas phase but a mixture in solution, while 1,9-diazabicyclo[7.3.1]tridecane (**55**) was entirely *in,out* under all conditions, with the 10-membered ring in a [2323] (or BCB) conformation as shown. The most interesting conclusion was that the onset of *in,out*-isomers is different in solution and in the gas phase, and this was ascribed to better solvation of the *out* than the *in* lone pairs.




## IV. Mechanisms for *In/Out* Interconversion: Homeomorphic Isomerization

Simmons and Park[1] pointed out that conformational interconversions of *out,out*- to *in,in*- and of *in,out*- to *out,in*-isomers are possible and require one of the three bridges to be threaded through the ring formed by the remainder of the structure. They called this process homeomorphic isomerization, although it is a conformational process, and this term has continued to be used. Park and Simmons found that *in,out*- and *in,in*-bicyclo[8.8.8]hexacosane (**6**) did not undergo homeomorphic isomerization,[15] and in fact only four well-established examples of homeomorphic isomerization have been reported. These examples occur in bicyclic ring systems of very different size and character, and so give interesting information on the structural requirements for the process.

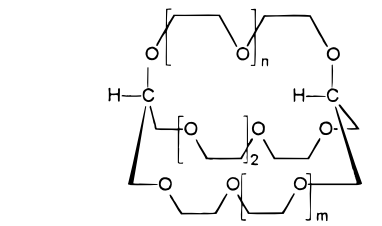
In the general case, a conformation resembling B in Figure 3 must be attained as an intermediate or transition state. In this conformation, the chain passing through the ring has much of the character of a catenane or rotenane, and it must make van der Waals contact with the surrounding ring. Examination of models and calculations show that this process only becomes practical for a bridge consisting of methylene groups when the ring through which the bridge is threaded contains more than 20 carbons or similar atoms. In the first reported case, Haines and Karntiang found examples of homeomorphic isomerization in *in,out*-isomers of macrocyclic cryptand-like compounds **56**−**59** with CH bridgeheads.[34] As can be seen, the approximate barriers, as determined by NMR, do not fall in a simple sequence of increasing ring size. The highest barrier, in **57**, is for a bicyclo-[12.10.9]triacontane, while the lowest barriers, associated with interconversion still being rapid at −70 °C, were found for [12.12.10] and [12.12.7] ring systems. It was suggested that (a) steric interactions between the central chain and the enclosing ring will be greater, the smaller that ring is, (b) the most favored transition state is one in which the chain passing through the enclosing ring is the one linking the secondary carbon atoms of the two glycerol residues, and (c) below a certain length for the latter chain, the shorter that chain is, the lower the barrier. It is clear that some of these factors are unique to the compounds considered, but Haines and Karntiang proposed the following explanation for point c. If one chain is appreciably shorter than the others, the angle $\theta$ (Figure 4) will be substantially greater than 0° in the ground state and this will, in effect, have moved this state some way toward the transition state (see below).

Kilburn et al.[78] have recently reported the isolation of two compounds, **60** and **61**, which are *in,out*-/*out,in*-isomers of one another, but are diastereoisomeric due to the presence of the aspartic acid moieties. These [15.11.11] macrobicyclic compounds slowly come to a 62:38 equilibrium with one another; at 50 °C in DMSO the half life is 4 h, giving an approximate activation energy of 22.7 kcal/mol. Solution conformations for each isomer were deduced from 500 MHz ROESY spectra and it was proposed that in the ground state one of the phenylene groups is sandwiched between the other phenylene group and the aminopyridine unit. It was suggested that the observed homeomorphic isomerization involved passage of the sandwiched chain through the ring made up of the other two chains.

Saunders and Krause report the homeomorphic isomerization of *out,out*- and *in,in*-bicyclo[6.5.1]-tetradecane (**16** and **17**), as discussed above, and also of *in*- and *out*-isomers of the bridgehead alkene bicyclo[6.5.1]tetradec-1(2)-ene.[37] In both cases, the preexponential factor corresponded to that expected for a unimolecular reaction, log *A* being 14.0 for the saturated hydrocarbon, and 15.5 for the alkene. The activation energy was quite high in both cases: $E_A$ was 24 kcal/mol for the saturated hydrocarbon, and 28 for the alkene. Nevertheless, the most striking feature is the smallness of the ring sizes which permit homeomorphic isomerization in these two cases as compared with the previous examples. It seems to the reviewers that a key factor here is that only a very short (one-carbon) bridge must pass through the other bridges. Since this single methylene group is already bonded to the bridgehead atoms it only needs to interact through van der Waals interactions with the atoms in one bridge. We also note that the angle $\theta$ (Figure 4) is quite large (∼78°) for *in,in*-bicyclo[6.5.1]tetradecane, providing some support for the proposal made by Haines and Karntiang.

The fourth example concerns the tricyclic tetramine **62**. Alder, Weisman, and co-workers[77] showed that geminal aminal hydrogen exchange occurs on the NMR time scale with a free energy of activation of 15.1 kcal/mol at 314 K. This process corresponds to net inversion of all three rings and must involve homeomorphic isomerization. Several mechanisms are possible, but the authors favoured an *in,out* → *out,in* process, rather similar to that observed by Saunders.

The interconversion of the macrobicyclic *in*- and *out*-ammonium ions reported by Simmons and Park

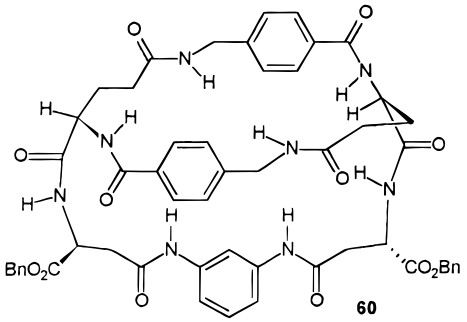


**56** n = 1, m = 1 $\Delta G^{\ddagger}$ 10.5 kcal/mol.

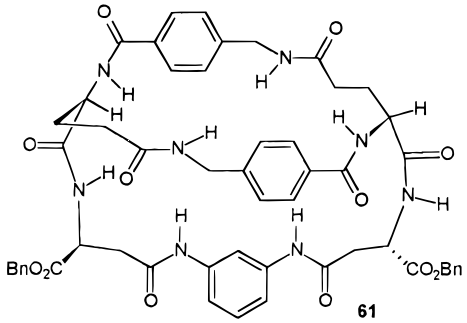
**57** n = 2, m = 1 $\Delta G^{\ddagger}$ 13

**58** n = 1, m = 2 $\Delta G^{\ddagger}$ >9

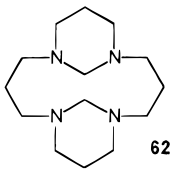
**59** n = 2, m = 2 $\Delta G^{\ddagger}$ >9



**60**



**61**



**62**

in their first papers occur by deprotonation/reprotonation reactions at the bridgehead nitrogen atoms, and not by homeomorphic isomerization. This is also true for the interconversion of all other ammonium ions of this type, e.g. **9** and **10**. The most important features of these interconversions are associated with the accessibility of the inside functionality, and so these reactions are discussed in section V.

## *V. The Accessibility of Inside Functionality*

One of the most interesting aspects of *in/out* isomerism is the accessibility of inside functionality to external reagents. In their original papers, Simmons and Park[1] found that the *out,out*-diprotonated ions of macrocyclic diamines were formed rapidly and were then only slowly isomerized to the *in,in*-isomers. Thus a 5:8 equilibrium mixture of diprotonated *out,out*-/*in,in*-isomers of 1,10-diazabicyclo[8.8.8]hexaeicosane is established in water in about 30 min, while in 50% trifluoroacetic acid equilibrium is almost completely on the *in,in* side, but is established much more slowly (presumably because the mecha-

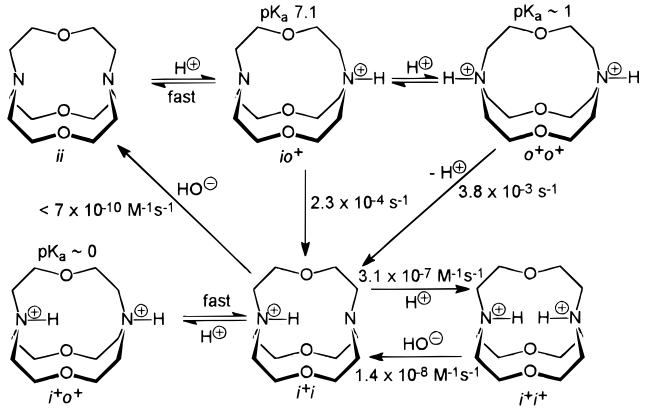



**Figure 5.** Rates and equilibria for outside and inside protonation of the [1.1.1]cryptand.[20]

nism of equilibration involves deprotonation, which is unfavorable in this more acidic solvent). Park and Simmons[2] estimated that the rate constants for the establishment of a hydrogen bond from water to an inside lone pair was $\sim 10^5$ times slower than for a typical tertiary amine, and the rate of proton transfer to an inside lone pair was at least $10^4$ times slower. These are large effects, even though the bridges in these bicyclic system are quite long. Many other examples of this type of behavior have been noted since, and the effects become much more dramatic in smaller ring systems.

The protonation behavior of the [1.1.1]cryptand (**9**) has been studied in great detail,[20] and the results are summarized in Figure 5. It can be seen that some of the rates are now very slow indeed. Most dramatically, the inside-monoprotonated ion $i^+i$ could not be deprotonated by hydroxide ion at all. It was estimated that the p$K_a$ for inside monoprotonation was greater than 17.8. X-ray structures of **9** and its inside protonated products have been reported, and it is clear that there is not a strong N···H—N$^+$ hydrogen bond in the $i^+i$ ion, although the proton certainly interacts with the oxygen atoms in the bridges.[21] Calculations on $i^+i$ and $i^+i^+$ by *ab initio* methods indicate that these may have unusual electronic properties.[79] The oxygen atoms may also assist in some of the proton transfer processes. One very interesting observation is that, while $i^+i$ could not be deprotonated by base, $i^+i^+$ could be converted back to the cryptand by treatment with solvated electrons (Na in liquid $NH_3$). This reaction may proceed by two-electron reduction to produce the cryptand containing a hydrogen molecule, which is then extruded.

The [2.2.2]cryptand has been very extensively studied and a full review of its properties is not attempted here.[8,9] The X-ray crystal structure of the di-protonated dication shows an *in,in*-chiral structure in which each proton is interacting with one nitrogen and three oxygens.[80] It seems that *in/out* conformational changes are not the rate-limiting steps on metal ion complexation by the [2.2.2]cryptand.[81]

Alder, Moss, and Sessions[82] studied the formation of intrabridgehead hydrogen-bonded ions from a series of medium-ring (1,*k*+2)diazabicyclo[*k.l.m*]-alkanes. Their results are summarized in Table 2. A number of the diamines (Table 2a) could be protonated by conventional proton transfer reactions

**Table 2. Inside Protonation of (1,*k*+2)-Diazabicyclo[*k.l.m*]alkanes**

(a) Bicyclic Diamines Inside Protonated by Conventional Proton Transfer Mechanisms

| *k*+*l*+*m*+2 | 1,2-diamino-ethane derivatives [*k.l.m*] | 1,3-diamino-propane derivatives [*k.l.m*] | 1,4-diamino-butane derivatives [*k.l.m*] |
|---|---|---|---|
| 13 | 6.3.2<br>5.4.2 | | |
| 14 | 6.4.2<br>5.5.2 | 6.3.3 | |
| 15 | | 6.4.3<br>5.5.3 | |
| 16 | | 6.5.3 | 5.5.4 |

(b) Bicyclic Diamines Inside Protonated by Redox-Promoted Intramolecular Processes

| *k*+*l*+*m*+2 | 1,3-diaminopropane derivatives [*k.l.m*] | 1,4-diaminobutane derivatives [*k.l.m*] |
|---|---|---|
| 13 | | |
| | 4.4.3 | |
| 14 | 6.3.3<br>5.4.3 | 4.4.4 |
| 15 | | 5.4.4 |
| 16 | 6.5.3 | 5.5.4 |

in $CDCl_3$ containing 1 equiv of $CF_3CO_2H$, although all these reactions were slow, typically requiring 0.5 h at 35 °C. All the diamines which were derivatives of 1,2-diaminoethane could be protonated in this way, along with some others. It was suggested that the key feature in these reactions was the accessibility of the inside lone pair. In diamines like 1,7-diazabicyclo[5.5.2]tetradecane (**63**), the angle between the lone pair director and the N···N axis ($\theta$) will be quite large, making the lone pair relatively accessible through the large ring (12-membered in this example). Protonation of these diamines was reversible, as expected.

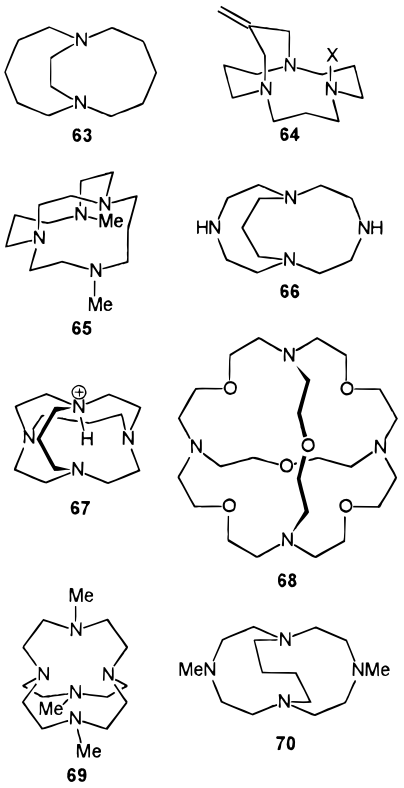
In another set of diamines (Table 2b), exemplified by 1,6-diazabicyclo[4.4.4]tetradecane (**10**), conventional proton transfer did not occur at all, and the proton, once inserted, could not be removed by base without destroying the compound. Most of these compounds will have very small values of $\theta$ ($\theta = 0°$ for **10**), and the lone pairs are extremely inaccessible. On the other hand the inside protonated ions, once formed, are likely to be very stable with strong intramolecular hydrogen bonds. In these circumstances an unusual redox-promoted process can occur in which the inside proton is not derived from the external acid, but comes off one of the $\alpha$-$CH_2$ groups, as established by deuterium labeling. The proposed mechanism for this process[25] involves an intramolecular hydrogen atom transfer to the bridgehead nitrogen cation radical.

In an ingenious development, Bell, Choi, and Harte[83] prepared 11-methylene-1,5,9-triazabicyclo-[7.3.3]pentadecane (**64**, X = H) and its 5-methyl derivative (**64**, X = $CH_3$) and found that these triamines immediately formed inside-protonated ions when trifluoroacetic acid was added to $CDCl_3$ solutions. Although the parent 1,9-diazabicyclo[7.3.3]-pentadecane is unknown, it does appear that protonation is unusually rapid in these substituted derivatives and it was suggested that this was due the third nitrogen atoms acted as a "proton relay". As expected, these compounds have a p$K_{a3}$ > 13.5, but low p$K_{a2}$ values, suggesting strong stabilization of the monoprotonated ion through hydrogen bonding.

Weisman *et al.*[84] prepared 4,11-dimethyl-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (**65**) by cross bridging the well-known macrocyclic ligand cyclam. They showed that this tetramine was more basic that DBU. A second protonation also occurred readily (p$K_{a2}$ 10.8), and the structure of the diprotonated ion showed two intramolecular hydrogen bonds, each between a bridgehead nitrogen and an N−Me group, within a diamond-lattice conformation having a cleft. The conformation also strongly complexed lithium, probably in a similar cleft. A number of related cross-bridged ligands have recently been reported.[85] Springborg *et al.*[86] have reported the preparation of a small bicyclic tetraaza-proton sponge, 1,4,7,10-tetraaza-bicyclo[5.5.3]pentadecane (**66**) and determined the structure of the dibromide perchlorate, in which the bridgehead nitrogen atoms share an inside proton, and the other two nitrogens are protonated, but well away from the intramolecular hydrogen bond. In keeping with this structure, the p$K_a$ for the monoprotonated ion (p$K_{a4}$) was estimated as >15, with p$K_{a3}$ 7.2, p$K_{a2}$ 3.2, and p$K_{a1}$ < −1, the last p$K_a$ being so low because the hydrogen bond has to be broken. It was not established whether the tetraprotonated ion is *in,out* or *out,out*. Springborg *et al.* have also been able to prepare the inside monoprotonated amine 1,4,8,11-tetraazatricyclo[6.6.2.$2^{4,11}$]octadecane (**67**),[87] a tetramine with a topology similar to that of **68** prepared by Graf and Lehn.[88] The structure of the aquatrichlorozincate(II) salt of **67** showed that this contains an inert proton coordinated inside a nearly tetrahedral tetramine cavity. The proton is between two of the bridgehead nitrogens, at distances of 1.38(9) and 1.35(9) Å, with the other two bridgehead nitrogens 2.29(9) and 2.13(9) Å away. They showed that this ion is aprotic in the pH range 0-14, and estimated that the exchange rate for the inside proton in 1 M NaOD must be less than $2 \times 10^{-8}$ $s^{-1}$ at 25 °C.

Micheloni and co-workers have examined the protonation properties of a number of small azamacrocycles.[89] Most of these systems are strong bases in the first protonation step and the proton exists inside the molecular cavity. The p$K_a$ for the inside monoprotonated ion of 4,10,15-trimethyl-1,4,7,10,15-pentaazabicyclo[5.5.5]heptadecane (**69**) is 11.8 (± 0.1) and the intrabridgehead nitrogen distance is 3.03 Å,[90] which is shorter than that observed in the inside monoprotonated ion of the [1.1.1]cryptand (3.60 Å). 4,10-Dimethyl-1,4,7,10-tetraazabicyclo[5.5.4]hexadecane (**70**) has also been prepared.[91] It behaves as a proton sponge and the first p$K_a$ could not be measured because it is too high. The intrabridgehead nitrogen distance in this inside monoprotonated salt is 2.75 Å, which is slightly longer in comparison with the inside monoprotonated ion of the similar compound 1,7-diazabicyclo[5.5.4]hexadecane (2.69 Å).[110] Some larger azamacrocycles have also been studied including 12,17-dimethyl-1,5,9,12,17-pentaazabicyclo-[7.5.5]nonadecane.[92,93]

The inside/outside protonation of *N*,*N*′-polymethylene-*syn*-1,6;8,13-diimino[14]annulenes in the gas phase has been shown to be chain length-dependent.[94]




There is rather limited information on the accessibility of inside C−H functionality. An unusual rearrangement of the *in*,*out*-bicyclo[5.3.1]undecan-11-yl radical was discovered[95] during the tri-*n*-butyltin hydride reduction of *in*,*out*-bicyclo[5.3.1]undecan-11-yl xanthate (**71**). Labeling studies showed that external hydrogen addition eventually occurred to give *out*,*out*-bicyclo[5.3.1]undecane, and suggested that a sequence of transannular hydrogen transfers occurred, one involving the inside hydrogen (Figure 6). Transannular hydrogen atom abstraction must also be involved in the unusual transformation of the *in*,*out*-acids **72** to the *out*,*out*-ketols **73**.[96] This reaction was not observed in the corresponding [4.3.1] and [5.3.1] systems.

With one exception, which will be discussed in section VI, the inside groups at the bridgeheads in bicyclic systems have been limited to hydrogens and lone pairs. In compounds like **14** and **15**, the double bond appears to lie perpendicular to the plane of the macrocyclic ring, so that both faces are shielded, making addition of bromine very slow. This is reminiscent of the betweenanenes.[97,98]

## *VI. Transannular Interactions Involving Inside Functionality*

Inside functionalities (restricted so far to lone pairs, H−C and H−$N^+$ groups) are placed in a molecular environment where intramolecular interactions are often not only entropically favorable but may be strongly driven by strain relief, especially in the smaller ring systems. These interactions resemble

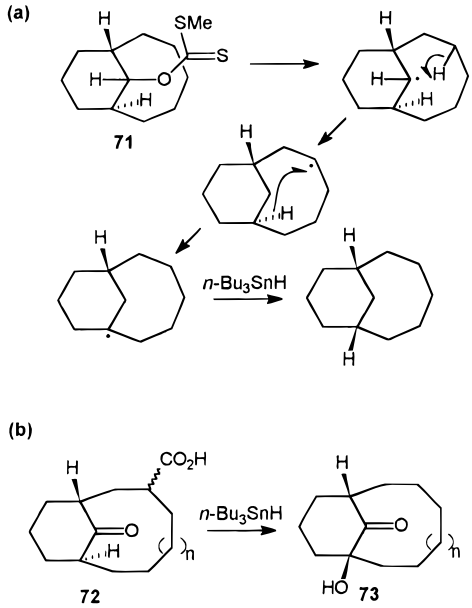



**Figure 6.** Transannular atom abstractions involving inside bridgehead hydrogen atoms: (a) tri-*n*-butyltin hydride reduction[95] of *in*,*out*-bicyclo[5.3.1]undecan-11-yl xanthate (**71**), (b) Barton decarboxylation[96] of *in*,*out*-3-carboxybicyclo[6.3.1]dodecan-12-one (**72**, $n = 1$) and *in*,*out*-3-carboxybicyclo[7.3.1]tridecan-13-one (**72**, ($n = 2$).

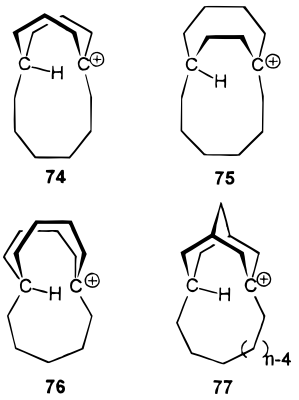
transannular interactions in monocyclic medium rings, but since there is often considerably greater strain relief to be gained by an interaction involving an inside bridgehead functionality, more extreme effects can often be observed. These types of interactions have been called intrabridgehead interactions, and they have been extensively reviewed.[23−25] For the purposes of discussion here, they will be divided into interactions involving (a) C−H groups, (b) lone pairs and H-$N^+$ groups, and (c) others interactions.

### A. Inside C–H Groups

In 1984, McMurry and Hodge[28] reported that protonation of *in*-bicyclo[4.4.4]-1-tetradecene occurred very easily to generate the *in*-bicyclo[4.4.4]-1-tetradecyl cation (**12**), a stable substance with a 3-center, 2-electron ($\mu$-hydrido) C−H−C bond. Further work showed that this carbocation could be generated to the extent of 50% in pure acetic acid.[29] This indicates a p$K_{R^+}$ of about 4, comparable to the tropylium ion. Examples of transannular $\mu$-hydrido bonds had been previously reported in the extensive work of Sorensen,[99] but these cations required superacids for their generation and were converted to other carbocations at quite low temperatures. The extraordinary kinetic persistence and thermodynamic stability of **12** must be due to the inaccessible nature of the inside hydrogen and also to strain relief associated with a decreased intrabridgehead distance on cation formation.

A remarkable feature of these $\mu$-hydrido cations is the chemical shift of the hydrido hydrogen, which occurs at extreme high field ($\delta$ −3.5 ppm for **12**), suggesting a $C^+$ $H^-$ $C^+$ polarization. In cation **12**, the C−H−C bond is presumably linear, and application of Saunders' isotopic perturbation method[100] and the $\Delta\delta(^1H,^2H)$ test of Altman and Forsén[101] showed that the C−H−C bond was truly symmetrical (single minimum). This is in agreement with calculations.[102]

In more recent work, a series of carbocations **74**−**76** with bent intrabridgehead 3-center, 2-electron C−H−C bonds have been generated by McMurry and Lectka,[57] and in related work, Sorensen and Whitworth[103] prepared a series of intrabridgehead tricyclic cations **77** ($n$ = 5−8). In the series **12**, and **74**−**76**, the C−H−C angle ranges from 180° to 113.6°, according to AM1 calculations, potentially allowing an increase in direct C···C bonding. The chemical shift of the bridging hydrogen moved to higher fields as the C−H−C angle decreased, reaching $\delta$ −5.6 ppm for **77** ($n$ = 5). It has been suggested that this shift is due to changes in the vibrational amplitude which accompany C−H−C bending.[102] In the series of cations studied by Sorensen and Whitworth, the nature of the hydrido bridge was found to depend strongly on the length of the variable bridge, and therefore presumably on the C···C distance. Thus while **77** ($n$ = 5) was clearly a $\mu$-hydrido-bridged cation, **77** ($n$ = 8) had an essentially normal tertiary structure.




McMurry and Lectka[104] discovered a remarkable alkane protonolysis reaction of the saturated *in,out*-bicyclo[4.4.4]tetradecane by acids. In $CF_3SO_3H/CH_2Cl_2$ at 0 °C, 90% of the theoretical amount of hydrogen was collected in 1 h and a clean solution of cation **12** was produced. A similar reaction was observed in the [6.3.3] ring system,[57] and both examples must be driven by the strain relief attendant on intrabridgehead bond formation.

## B. Inside Lone pairs and H–N$^+$ Groups

The inside protonation of bridgehead diamines, described above, leads to ions which may exhibit very strong intrabridgehead hydrogen bonding. This is shown by extreme downfield chemical shifts for the N−H protons, and unusual IR absorption spectra. This area has been reviewed,[25] and so discussion here will be quite brief. The X-ray crystal structures of salts of a range of these ions have been determined: [4.4.4],[105] [6.4.3],[106] [5.4.3],[107] [5.5.2],[108] [6.5.3],[109] [5.5.4],[110] [5.4.2].[111] The N−H−N angles range from 180° for the symmetrical [4.4.4] case to 132° for the [5.4.2]. The IR and NMR spectra of the ions have been correlated with the structural data and the question of single vs double minimum potentials has been discussed.[112] Other examples of intrabridgehead hydrogen bonds are discussed in section V.

Many of these medium-ring bicyclic diamines show unusually low ionization energies in photoelectron spectra[74,75] and are exceptionally easily oxidized. In some cases, oxidation in solution produces radical cations which are long-lived and even stable enough for X-ray crystal structures of salts to be determined as in the case of the radical cation of **10**.[113] Further oxidation of these radical cations leads to propellanes, with a full 2-electron bond between the bridgehead atoms. Structures were also obtained for the radical cations of *N,N′*-trimethylene-*syn*-1,6;8,13-diimino[14]-annulene (**45**)[114] and *N,N′*-tetramethylene-*syn*-1,6;8,-13-diimino[14]annulene (**46**).[68] ESR and ENDOR studies of these species have been carried out,[115,116] and a good correlation of the hyperfine coupling constant $a_N$ with the average C−N−C angle established.[68]

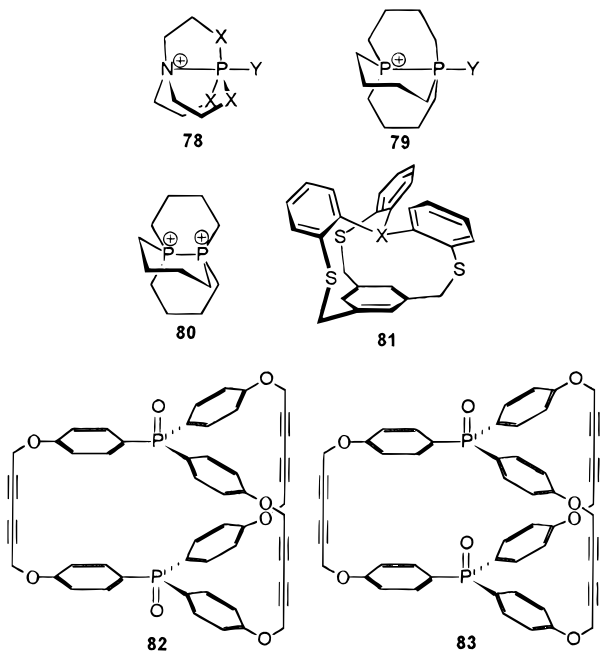
## C. Other Interactions

A very limited number of interactions involving other elements have been studied. Verkade has demonstrated a gradation of hypervalent P···N interactions in compounds with a [3.3.3] skeleton like **78**.[117,118] The P···N distance varied from 1.9 to 3.2 Å depending on the apical substituent Y on phosphorus. The geometry at the nitrogen atoms varied from being pyramidal inward in those compounds with a short P···N distance to being more or less flat when there was little P···N bonding. At the same time the phosphorus went from being a trigonal bipyramid to being tetrahedral outward. Compounds with an apical hydrogen are very weakly acidic, which means that the free PN base is extremely strong.

A series of nucleophilic adducts **79** to dication **80** have been described, in which $J_{PP}$ varied from 47 Hz when Y = $PhCH_2$ to 182 Hz when Y = F.[119,120] No structures have been reported,[121] but it seems likely that there is again a gradation of distances between the bridgehead atoms, accompanied by changes in geometry. However, in this larger [4.4.4] system, it was thought that the lone pair on the phosphorus atoms was still inside even for the benzyl adduct. This compound does, however, react with benzyl bromide at high temperature to give the *out,out*-dibenzyl dication. As with Verkade's compounds, the adduct with Y = H was very difficult to deprotonate.

Pascal and co-workers have studied the interaction between an inside Si−H group and the benzene ring in the silaphane **81** (X = SiH) and the corresponding interaction in the phosphaphane **81** (X = P).[122] The silicon compound was characterized by a high field SiH at $\delta$ 1.04, 5 ppm upfield of an acyclic model, and by a Si−H stretching band at 2457 $cm^{-1}$, 280 $cm^{-1}$ above the acyclic model. In the phosphorus compound, the benzene ring carbon atoms exhibited through-space coupling to the phosphorus atoms ($J_{PC(methine)}$ 7.5 Hz, $J_{PC(quaternary)}$ 3.5 Hz). The phosphorus atom was quite unreactive, not being protonated by HBr. Oxidation with refluxing hydrogen peroxide and acetic acid yielded the trisulfone, without formation of the phosphine oxide. Related compounds with nitro-substituted basal aromatic rings are colored, probably due to charge-transfer interactions.[123]

Friedrichsen and Whitlock[124,125] have prepared the macrobicyclic compounds **82**, in which the bridgehead phosphine oxides are outside the molecular cavity

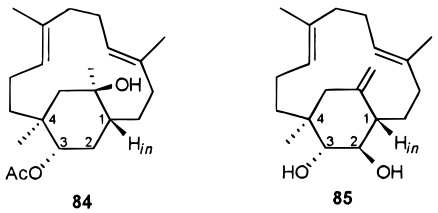



and **83**, in which one of the bridgehead phosphine oxides was directed inside the molecular cavity. In addition, the acetylenic groups of both of these systems were reduced to give the corresponding saturated compounds. The complexation behavior of all of these macrocycles has been investigated and complexation inside the molecular cavity has been demonstrated with a variety of neutral organic guests.

## *VII. Natural Products Showing In/Out Isomerism*

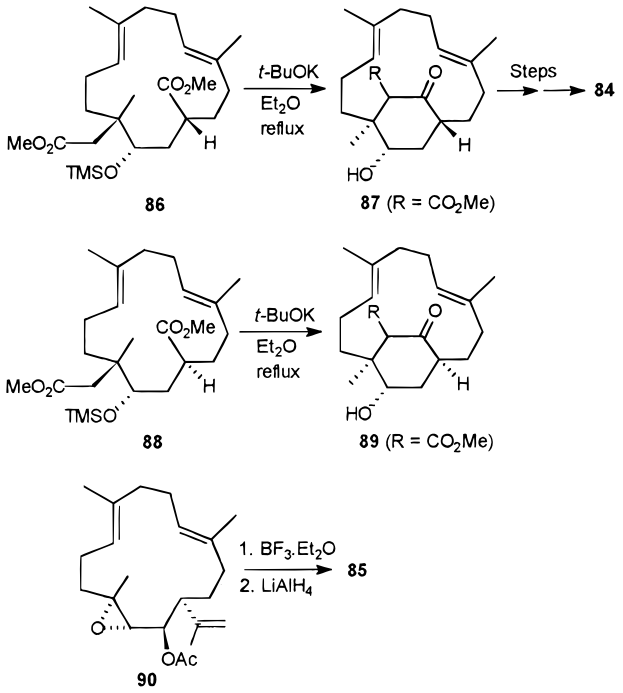
Few known natural products exhibit the phenomenon of *in/out* isomerism, but the presence of this interesting structural feature in complex molecules presents a considerable challenge to the synthetic chemist and so has received widespread attention.

3α-Acetoxy-15*β*-hydroxy-7,16-secotrinervita-7,11-diene (**84**)[126] and secotrinerviten-2*β*,3α-diol (**85**)[127] belong to the secotrinervitane class of diterpenoids and have been isolated from the defence chemicals secreted by soldiers of the nasute termite species. The *in/out* isomerism of these bicyclic diterpenes results from a *trans* diequatorial configuration of substituents at C(1) and C(4) in the cyclohexane ring.



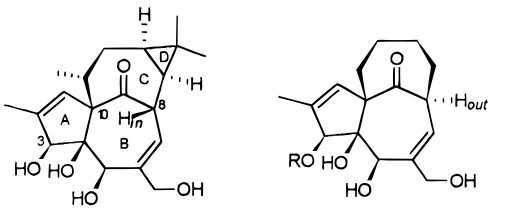

Kato and co-workers have developed a synthesis of (±)-**84**[128,129] and (±)-**85**[130,131] and prepared nonnatural product seconitervitanes that also show *in/out* isomerism.[131,132] The key steps in these synthetic routes rely on the construction of the cyclohexane ring with correct relative stereochemistry. The *in/out* configuration of (±)-**84** was accomplished using an intramolecular Dieckmann condensation of substrate **86** to give the keto ester **87**. In an analogous reaction the stereoisomeric *out,out* keto ester, **89** was also prepared.

The *in,out* stereochemistry observed in (±)-**85** was achieved by an intramolecular cyclization of **90**, promoted by treatment of the epoxide with $BF_3{\cdot}Et_2O$. Replacement of the acetate protecting group at C(2) with an ether protecting group and treatment with $BF_3{\cdot}Et_2O$ under similar conditions provided other seconitervitanes with *in,out* stereochemistry.[131] However, investigations on stereoisomeric epoxides which might be expected to give the nonnatural product compounds with *out,out* stereochemistry were unsuccessful.




Ingenol (**91**) is a highly oxygenated tetracyclic compound belonging to the ingenane family of diterpenes. Various esters of ingenol have been isolated from plants of the genus *Euphorbia* (e.g. the C(3) hexadecanoate[133]) and many of these are known to have tumor-promoting properties because of their high affinity for protein kinase C. The structure contains a bicyclo[4.4.1]undecan-11-one ring system (rings BC) which possesses the *in,out* intrabridgehead stereochemical relationship at C(8) and C(10).

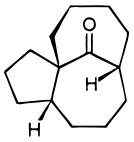
Considerable effort has been invested in developing synthetic routes toward the ingenanes and ultimately to devise a total synthesis of ingenol. Most of the initial studies have postponed the solution to the *in,out* or *trans* stereochemistry observed in the natural product, and focused on procedures to build the basic ingenane skeleton with an *out,out* or *cis* intrabridgehead stereochemical relationship since this isomer is expected to be less strained. Paquette and co-workers have prepared the highly functionalized 8-isoingenoid (**92a**).[134] The key step to introduce the intrabridgehead stereochemistry involves an alkylation/cyclization of **94** with (*Z*)-1,4-dichloro-2-butene to give tricyclic **95** (Figure 7a).[135] A later step involving photoisomerization of an α,*β*-epoxy ketone affords the ABC ring system present in ingenol. Preliminary biological studies on the C(3) palmitoylate ester, **92b** found it to be inactive.[136]



**91**



**92a** (R = H)
**92b** (R = $C_{15}H_{31}CO$)



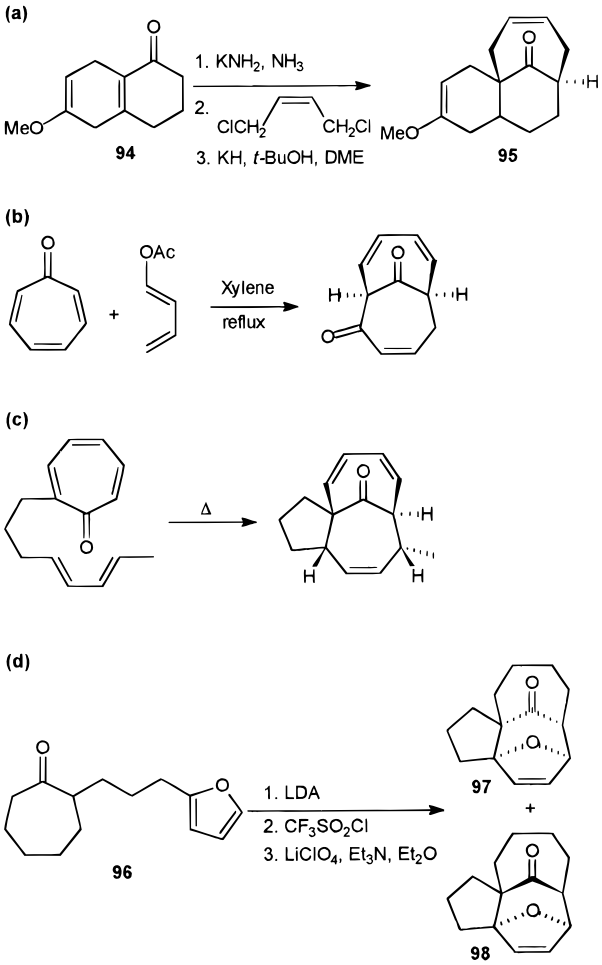
**93**

Rigby has developed a route to construct the tetracyclic skeleton of ingenol utilizing an intermolecular [6 + 4] thermal cycloaddition reaction to give the important bicyclo[4.4.1]undecan-11-one system (Figure 7b).[137−139] Again the intrabridgehead stereochemical arrangement in this product is *cis*.

Funk has explored the intramolecular variation of a [6 + 4] cycloaddition which has also provided a route toward the *out,out* ingenane isomer (Figure 7c).[140]

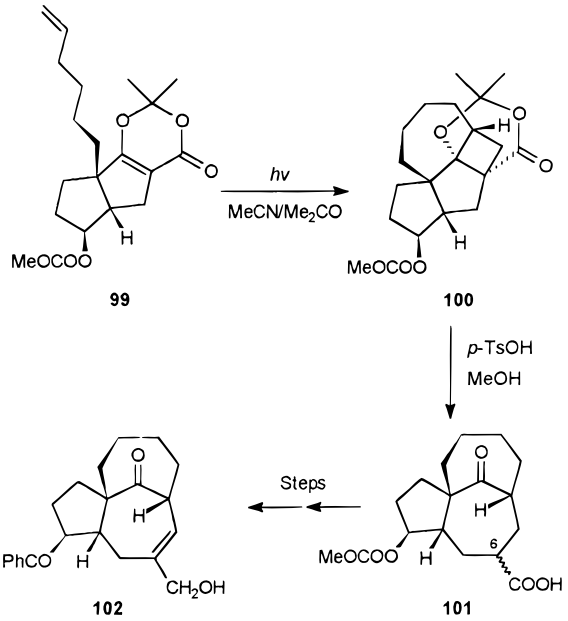
The ABC ring skeleton in ingenol has also been constructed by Harmata.[141] The methodology used in this investigation employs an intramolecular [4 + 3] cycloaddition of a cyclic oxyallyllic species generated from ketone **96** with the attached furan. This provides the *out,out* exo **97** and endo **98** isomers in a 7.3:1 ratio (Figure 7d).

Winkler has successfully accessed the bicyclo[4.4.1]-undecan-11-one system containing the correct *in,out* stereochemistry at the bridgehead atoms by applying his method of intramolecular [2 + 2] photocycloaddition of alkenes and dioxenones.[142] Preliminary investigations provided **25** (BC rings) and **93** (ABC rings),[143,144] but more recently the methodology has been modified to introduce additional functionality at C(3).[145,146] The photoadduct **100** was prepared from dioxenone **99** and fragmentation under acidic conditions formed **101** as an epimeric mixture at C(6). From this synthetic route Winkler has developed the first ingenol analogue, **102** which has a high affinity for protein kinase C. The activity of **102** compared with **92b** is probably a result of the *in,out* stereochemical relationship in **102**, matching that observed in the natural product.



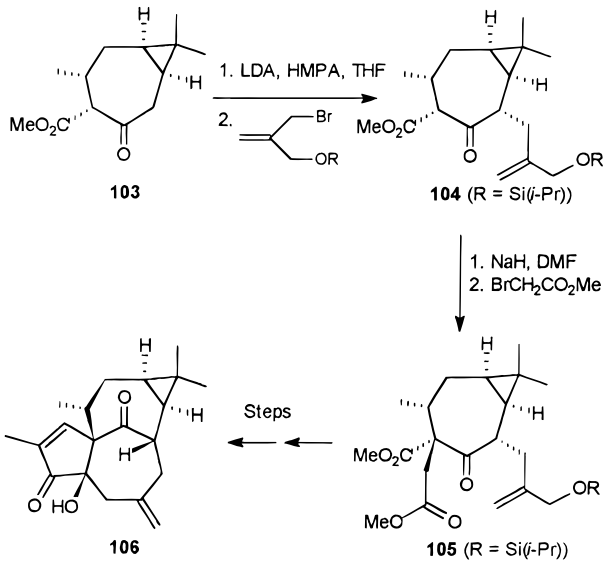

**94** **95** **96** **97** **98**

**Figure 7.** Synthesis of *out,out*-ingenane analogs by (a) alkylation/cyclization of **94** to give tricyclic **95**,[132−134] (b) intermolecular [6 + 4] thermal cyclocloaddition,[135−137] (c) intramolecular [6 + 4] thermal cycloaddition,[138] (d) intramolecular [4 + 3] cycloaddition.[139]




**99** **100** **101** **102**

Funk and co-workers have also addressed the *in,out* intrabridgehead stereochemistry of the ingenol system. The synthetic strategy adopted in their studies relies on the stereoselective attachment of two functionalized side chains to a cycloheptanone ring **103** to give the *trans* arrangement at C(8) and C(10) (ingenol numbering) in **105**. Subsequent steps including a lactonization and Claisen rearrangement-based ring contraction affords the ingenol skeleton. Initial investigations allowed the construction of the BCD rings,[147] and more recently, modifications of the side chains has enabled the effective incorporation of the A ring, and the tetracyclic ingenol analogue **106** has been synthesized.[148]




## VIII. Conclusions

Inside/outside isomerism is a simple and graphic concept which has proved its worth by generating some very interesting chemistry during the last 25 years. Much of the interest in this area lies in the unusual properties of functionality hidden inside the ring system and this often depends on the degree of "in-ness" and "out-ness" of the bridgehead substituent, as measured by the angle $\theta$ (Figure 4). It seems to the present reviewers that it is more appropriate to use *in/out* as a useful description of conformation like "chair" or "twist" rather than to strive for its incorporation into the strict rules of nomenclature. We believe that the idea will continue to provide a useful way of looking at a number of interesting phenomena.

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