Neighbouring Group Participation in *N*-Methoxymethyl 7-Azanorbornanes 1: The Synthesis of *N,N'*-Methano-bridged Diazasesquinorbornanes, N^3-[3]Polynorbornanes and CN^3-[4]Polynorbornanes

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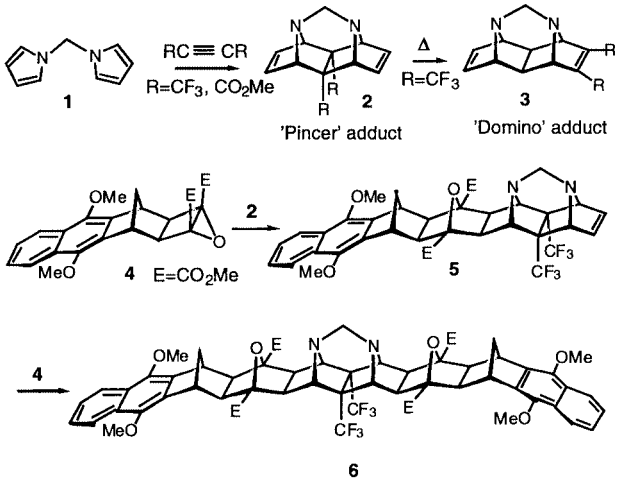
Abstract: A new tandem route to *N,N'*-methano-bridged diazasesquinorbornanes is reported in which 7-azabenzonorbornadienes are reacted with ester-activated *N*-(methoxymethyl)aziridinocyclobutanes to form adducts which immediately undergo *N,N'*-methano-bridge formation by nucleophilic attack of the nitrogen lone pair of one *N*-bridge onto the methoxymethyl group attached to the adjacent *N*-bridge. Alternative routes to *N,N'*-methano-bridged structures of this type are discussed.

Key words: neighbouring-group, cycloadditions, bicyclic compounds, stereoselectivity

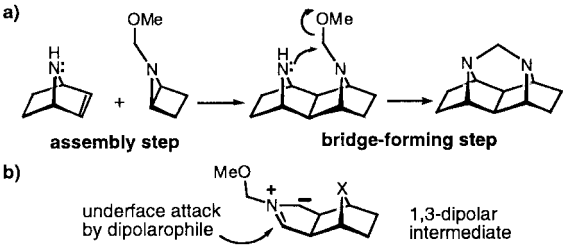
N,N'-Methano-bridged diazasesquinorbornanes are a rare class of aza-alicyclic compounds which were first described in 1985 by Visnik and Battiste who reported that addition of perfluorobut-2-yne or dimethyl acetylenedicarboxylate (DMAD) to *bis*-(*N*-pyrrolyl) methane **1** (Scheme 1) produced exclusively the pincer adducts **2** and that these could be isomerised to domino-adducts **3** upon heating.[1]



Previous work in the field of *N,N'*-methano-bridged diazasesquinorbornane synthesis

Scheme 1

As part of our block building program for scaffold construction,[2,3] we examined **2** ($R = CF_3$) as a *bis*-alkene block to incorporate the *N,N'*-methano-bridged diazasesquinorbornane subunit into a [n]polynorbornane framework. In practice, *bis*-alkene **2** resisted almost all attempts to achieve Diels-Alder, 1,3-dipolar or ruthenium-catalysed [2+2] addition at one or both π-bonds. The exception was the photochemically-induced 1,3-dipolar addition of epoxide **4** to **2** ($R = CF_3$) which produced the mono-adduct **5** and the *bis*-adduct **6**.[4] Attempts to build onto the π-bonds of mono-adduct **5** or the domino adduct **3** were equally unrewarding. Accordingly, we have developed a new approach to the synthesis of *N,N'*-methano-bridged diazasesquinorbornanes in which the methano-bridge is formed as the second part of a tandem sequence in concert with the [n]polynorbornane construction regime,[3a] and this is the subject of the present communication.

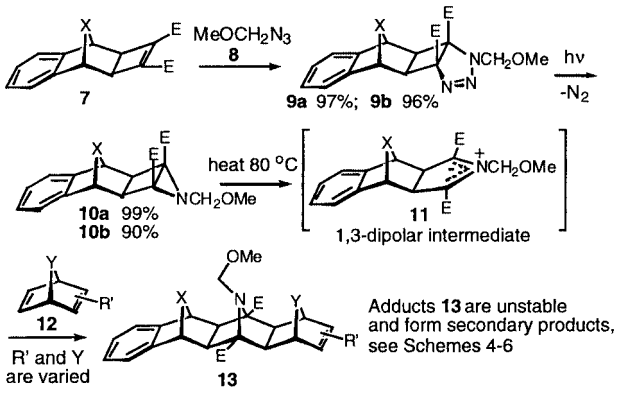


a) Stepwise assembly process and b) origin of 1,3-dipolar cycloaddition stereoselectivitiy

Scheme 2

The reaction leading to the formation of the intermediate *N*-(methoxymethyl) diazasesquinorbornane **13** was envisaged to occur by 1,3-dipolar cycloaddition of an appropriate 7-azanorbornene acting as the dipolarphile with an *N*-(methoxymethyl)aziridine. In practice, intramolecular displacement of methoxide occurred spontaneously by participation of the neighbouring bridge-nitrogen lone pair to form the *N,N'*-methano bridged products (Scheme 2a). As outlined in the reaction pathway shown in Scheme 3, the participating *N*-bridge component could be introduced into the [3]polynorbornane **13** either from the aziridine reagent, i.e. **10a** or as part of the dipolarophile, i.e. **12** (Y = NR). In both cases, 1,3-dipolar cycloadditions were anticipated to occur with *exo,exo*-stereoselectivity by underface attack on the dipole (Scheme 2b) to afford the *syn*-facial XNY-[3]polynorbornane adducts **13a,b**, in which the central *N*-bridge bears the methoxymethyl

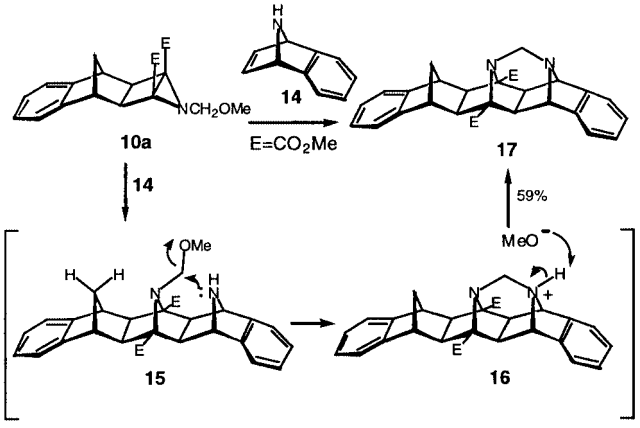
substituent and is set up for intramolecular cyclisation (X = NR or Y = NR) to furnish the desired *N,N*-methano-bridged diazasesquinorbornane subunit.



Preparation of aziridino cyclobutanes and reaction with norbornadienes. Series a) X = CH_2: b) X = NZ.

Scheme 3

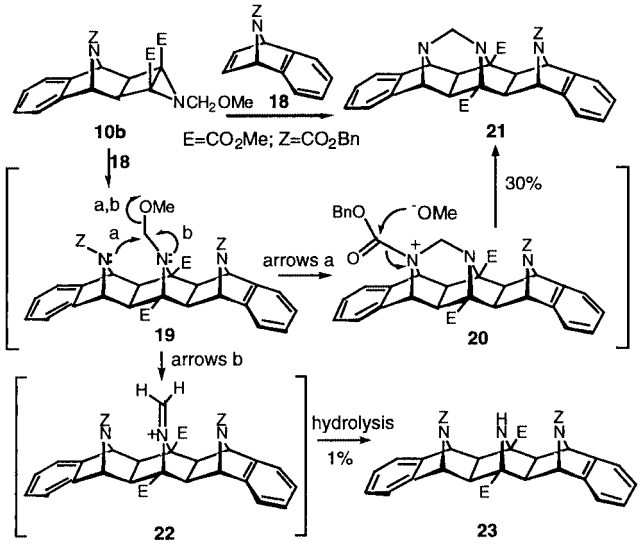
Preparation of the required *N*-(methoxymethyl)aziridines **10a,b**[12] was achieved by addition of methoxymethyl azide **8** to the appropriate cyclobutene-1,2-diesters **7a,b** followed by deazetisation of the resultant triazolines by ultraviolet irradiation.[3a,5] The first route was illustrated by reaction of 7-azabenzonorbornadiene **14** (Scheme 4) with the methano-bridged *N*-(methoxymethyl)aziridino cyclobutane **10a** (benzene at reflux for 3 hours) to afford the *N,N'*-methano-bridged CN^2-[3]polynorbornane **17**[12] in 59% yield. The 1:1-adduct **15** is the presumed intermediate and cyclisation (arrows on **15**) requires the N-invertomer to be proximate to the NH-bridge. Significantly, this is the preferred invertomer geometry in the related *N*-benzyl CN^2-[3]polynorbornane.[3a]



Preparation of *N,N'*-methano-bridged CN^3-[3]polynorbornadiene **17**

Scheme 4

The second method is demonstrated using the aza-bridged *N*-(methoxymethyl)aziridinocyclobutane **10b** (Scheme 5). In this case, reaction of the Z-protected benzo-7-azanorbornadiene **18** with **10b** produced, somewhat surprisingly, the *N,N'*-methano-bridged product **21**[12] directly. Clearly, the Z-group is lost in the course of the methano-bridge formation from the initially-formed adduct **19** (Scheme 5). The mechanism proposed in Scheme 4 for this process has some interesting features since it involves nucleophilic attack by the nitrogen of the *N*-Z bridge in adduct **19** and requires that it has non-planar geometry.[6] There is evidence for the terminal *N*-Z bridge of N^3-[3]polynorbornanes being able the adopt the non-planar geometry depicted in **19** based on X-ray data for the corresponding *N*-benzyl system.[7,8] A consequence of the non-planar geometry is the attendant loss of resonance stabilisation typical of the planar system and so the bridge nitrogen should become more nucleophilic. This should favour attack by the *N*-bridge lone pair onto the adjacent *N*-methoxymethyl to form the *N,N'*-methano-bridge (**19** to **20**, arrows a). In a second step, attack by the concommitantly generated methoxide ion onto the Z-group of **20** would effect removal of that group.



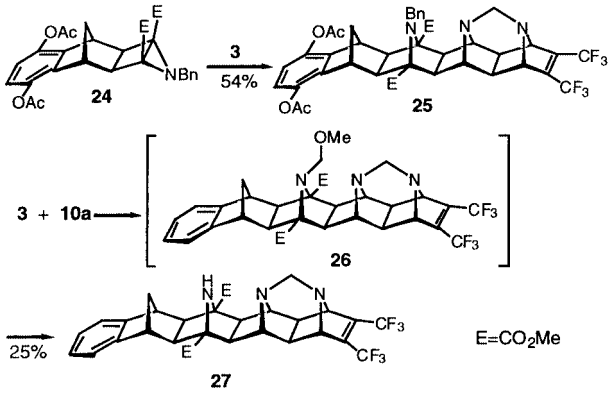
Synthesis of *N,N*-methano-linked N^3-[3]polynorbornadiene **21** and deprotected byproduct **23**

Scheme 5

It has been established in the *N*-benzyl series that significant flattening of central *N*-bridge occurs when flanking bridges are present in XNY-[3]polynorbornanes and that when X = Y, dynamic invertomerisation of the *N*-substituent occurs at room temperature.[3a,3b] It is reasonable to expect a similar situation can exist in **19** and that the *N*-methoxymethyl substituent is rapidly interconverting between the two invertomers. This compression towards planar nitrogen would lower the transition state energy (ground state effect) for vicinal elimination of methoxide from **19** (arrows b) to form iminium ion **22**. While we do not consider that **22** is an intermediate in the formation of **20**, it does present itself as a plausible intermediate in the formation of NH compound **23**[12], which is isolated as a

minor byproduct in this reaction. Formation of **23** involves a hydrolysis step and preliminary evidence indicates that this probably occurred in the course of chromatographic workup.[9] Interestingly, the de(methoxymethylation) step becomes the major pathway in *N*-methoxymethyl XNY[3]polynorbornanes where intramolecular cyclisation is no longer available and has been used to prepare CN-bridged compounds where X or Y = isopropylidene (see also formation of **27**, Scheme 6).[8]

As mentioned in the introduction, direct addition to the π-bond of alkene **2** has not proved to be a fruitful route to functionalised *N,N'*-methano-bridged [n]polynorbornanes. Limited success was forthcoming from the reaction of the aziridine **24** with the pincer adduct **2**, however, the 1:1-adduct (m/z = 813.2475) that is formed lacks the olefinic protons expected for a product derived directly from **2**. The ^{1}H and ^{13}C NMR spectral data support structure **25** (Scheme 6) which is considered to be derived from addition to the domino adduct **3**, generated from **2** under the thermal reaction conditions. A similar reaction of the *N*-(methoxymethyl)aziridine **10a** with **2** also follows this path and leads to the formation of **27** (m/z = 607.1882), a deprotected form of the initially-formed adduct **26**. Disappointingly, attempts to form a product with four *N*-bridges by reaction of aziridine **10b** with **2** were not rewarding.[10]



Rare example of pincer diene **3** acting as a dipolarophile in CN[3]-[4]polynorbornane formation

Scheme 6

In conclusion, this ability to prepare *N,N'*-methano-bridged compounds either by direct cycloaddition or by neighbouring group participation opens up entry to a versatile range of entirely new hetero-bridged [n]polynorbornane frames. Such scaffolds can be used to modify topology since molecular modelling shows that they are less curved than the compounds lacking the *N,N*-methano-bridge.[11] The *N*-bridges are locked into a geometry corresponding to the highly disfavoured *syn,syn*-invertomer geometry of diazasesquinorbornanes, a feature which can be exploited in the molecular design of polarofacial scaffolds. The neighbouring group participation route is not restricted to N-C-N bridges and other examples will be reported in due course.

Acknowledgement

We thank Mr Malcolm Hammond for conducting some of the developmental work on the synthesis of *N*-(methoxymethyl)aziridines. GS and MH thank Central Queensland University for the award of a CQU PhD scholarship.

References and Notes

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(12) Representative spectral details of new compounds: **10b** ^{1}H NMR ($CDCl_3$ at 60 °C) δ 2.36 (2H, s, H9,13), 3.50 (3H, s, OMe), 3.77 (6H, s, $CO_2Me \times 2$), 4.20 (2H, s, NCH_2O), 5.03 (2H, s, CH_2Ph), 5.76 (2H, s, H1,8), 7.16-7.44 (9H, m, aromatic). ^{13}C ($CDCl_3$ at 60 °C) δ : 52.9, 57.7, 61.3, 62.1, 67.6, 80.8, 112.9, 121.3, 127.3, 128.2, 136.9, 156.4, 167.2, 183.6. HRMS m/z calcd for $C_{26}H_{27}N_2O_7$: 478.1740, found 478.1721. **17:** mp 207-208 °C ^{1}H NMR ($CDCl_3$) δ (ppm): 1.45 (1H, d, *J* = 8.9 Hz), 1.87 (2H, s), 2.07 (2H, s), 3.10 (2H, s), 3.20 (1H,

d, *J* = 8.9 Hz), 4.02 (6H, s), 4.20 (2H, s), 4.27 (2H, s), 7.03-7.25 (8H, m), ^{13}C NMR ($CDCl_3$) δ (ppm): 44.5, 47.1, 50.6, 52.7, 54.4, 63.5, 67.5, 75.9, 120.4, 121.8, 126.2, 127.0, 145.2, 149.1, 171.7. HRMS m/z calcd for $C_{28}H_{26}N_4O_2$: 454.1893, found 454.1901.

21 mp 135-137 °C. ^{1}H NMR ($CDCl_3$) δ 2.20 (2H, s, H2,11), 2.14 (2H, s, H13,22), 3.80 (3H, s, E), 4.07 (3H,s, E), 4.18 (1H, s, H21), 4.23 (1H, s, H14), 4.39 (1H, d, *J* = 14.7 Hz, NC*Ha*HbN), 4.50 (1H, d, *J* = 14.7 Hz, NCHa*Hb*N), 5.00 (1H, d, *J* = 12.5 Hz, C*Ha*HbPh), 5.04 (1H, s, H3/10), 5.14 (1H, d, *J* = 12.5 Hz, CHa*Hb*Ph), 5.14 (1H, s, H10/3), 7.08-7.32 (13H, m, aromatic). ^{13}C NMR ($CDCl_3$) δ 451.01, 51.05 (C13, C22), 52.81, 53.17 (CO_2*Me*, CO_2*Me*), 54.13, 54.59 (C2,C11), 62.29, 62.57 (C3,10), 63.74 (C26), 67.20 (Bn), 67.35, 67.41 (C14, C21), 75.32, 75.38 (C1,12), 120.22, 120.68 (C5,8, C16,19), 127.40, 127.47 (C6,7, C18,19), 128.33, 128.48, 128.90, C2',3',4' of Bn, 137.76 (C1' of Bn), 145.29, 145.32, 145.60, 145.78 (C4,C9,C15,C20), 153.21 (*C*O_2Bn), 171.75, 171.80 (*C*O_2Me, *C*O_2Me). HRMS $C_{35}H_{31}N_3O_6$ requires 589.2213, found 589.2219.

23 mp 160-161 °C. ^{1}H NMR ($CDCl_3$) δ 2.03 (4H, s, H2,11, 13,22), 3.83 (6H, s, 2 × CO_2Me), 5.04 (4H, s, 2 × C*H*$_2$Ph), 5.15 (4H, s, H3,10,14,21), 7.06-7.35 (18H, m, aromatic)

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