Bromination of *exo*- and *endo*-Tricyclo[3.2.1.0^{2,4}]octane

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Reaction of *exo*-tricyclo[3.2.1.0^{2,4}]octane with bromine in CCl_4 or methanol proceeds, at least in part, by way of a classical ion to give 1,3-addition products. Electrophilic attack by bromine occurs with inversion at the corner to the C2C4 bond and nucleophilic attack by both inversion and retention. In methanol the initial cation species is sufficiently short lived that it does not relax to the classical cation, and nucleophilic attack with inversion competes with skeletal rearrangement. Reaction of *endo*-tricyclo[3.2.1.0^{2,4}]octane with bromine in CCl_4 gives 1,3-addition and an addition rearrangement product which are formed with inversion at the site of both electrophile and nucleophile attack. A further dibromide product is observed, the formation of which is suppressed in methanol. In methanol nucleophilic attack occurs with inversion to give a mixture of 1,3-addition and rearrangement products.

Introduction

The difficulty and importance attached to functionalizing hydrocarbons by chemical means is well recognized. Understanding reactions where selective carbon–carbon σ-bond rupture is known to occur is important if the chemistry of carbon–carbon σ-bonds is to be developed. The ring strain of cyclopropanes gives substrates that contain this functionality a chemistry that resembles alkenes rather than other cyclic hydrocarbons[1] and allows 1,3-functionalization of the skeleton by rupture of a carbon–carbon σ-bond. The carbon–carbon bond of cyclopropanes can be involved in pericyclic, radical, and ionic reactions as well as undergo addition reactions with organometallic compounds. Many studies directed toward the use of this functional group in organic synthesis[2] have examined the influence of substituents on geometry,[3] electronic structure,[4] reactivity, stereochemistry, and regiochemistry.

Our previous studies of *exo*- and *endo*-tricyclo[3.2.1.0^{2,4}]-octanes and tricyclo[3.2.1.0^{2,4}]oct-6-enes with proton acids[5] and mercuric acetate[5c,6] have established the stereochemistry and regiochemistry of addition. For example, with acid and mercuric acetate *endo*-tricyclo-[3.2.1.0^{2,4}]oct-6-ene and the 2-methyl derivative show a regiochemical preference for exclusive reaction at the cyclopropane ring in preference to reaction at the double bond. In conflict with the Markovnikov rule for opening of cyclopropanes[7] electrophilic attack occurs with internal cyclopropyl bond (C2–C4) rupture and inversion of configuration at the site of electrophilic attack; a process referred to as corner attack.[5c,6] This contrasts with *exo*-tricyclo[3.2.1.0^{2,4}]oct-6-ene where mercuration occurs predominantly at the double bond (89%) and protonation of the alkene also competes (18%) with cyclopropane ring opening. The differing geometrical constraints imposed on the cyclopropane ring in *exo*- and *endo*-tricyclo-[3.2.1.0^{2,4}]octanes and *exo*- and *endo*-tricyclo[3.2.1.0^{2,4}]oct-6-enes results in different orbital interactions of the cyclopropane with the rest of the hydrocarbon skeleton and thus with reacting electrophiles.

The current study is an extension of our investigation[5,6] of the stereochemistry of the reactions with the electrophiles proton, deuteron, and mercuric acetate. Herein we report the regio- and stereoselectivity of the addition of bromine with *exo*-and *endo*-tricyclo[3.2.1.0^{2,4}]octane.

Results and Discussion

Bromination reactions of simple cyclopropanes have been studied[8,9] in some detail. Skell et al.[8] argued that "the mechanism of reaction is one of backside attack by bromine to produce a free carbonium ion which is involved in a competition between rearrangement, loss of a proton, and collapse with bromide ion." Reactions are known where the first step of the reaction, the attack of the electrophile, occurs exclusively with either inversion or retention and others where retention and inversion compete.[10] A most notable study by Lambert et al.[11] on deuterated cyclopropanes concluded that "both bromine and chlorine appear to attack cyclopropane at the edge with retention, and the resulting halonium ion then is attacked by halide ion with inversion to form product."

Although radical reactions of bromine with cyclopropanes are known to occur rapidly in nonpolar solvents[8] the possibility of radical induced reaction was minimized by carrying out the reactions in the dark. As CCl_4 was the reaction solvent[12] and the probability of collision with solvent is greater than with bromine, significant amounts of chloride-containing products would

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(1) de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 809.

(2) Reissig, H.-U. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley and Sons: Chichester, 1987; Chapter 8.

(3) Allen, F. H. *Acta Crystallogr.* **1980**, *B36*, 81.

(4) Hoffmann, R. *Tetrahedron Lett.* 1970, 2907. Günther, H. *Tetrahedron Lett.* **1970**, 5173. Clark, T.; Spitznagel, G. W.; Klose, R.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1984**, *106*, 4412.

(5) (a) Coxon, J. M.; Steel, P. J.; Whittington, B. I. *J. Org. Chem.* **1989**, *54*, 1383. (b) Coxon, J. M.; Steel, P. J.; Whittington, B. I. *J. Org. Chem.* **1989**, *54*, 3702. (c) Coxon, J. M.; Steel, P. J.; Whittington, B. I. *J. Org. Chem.* **1990**, *55*, 4136. (d) Coxon, J. M.; Steel, P. J.; Whittington, B. I.; Battiste, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 2988.

(6) Burritt, A.; Coxon, J. M.; Steel, P. J. *Trends in Organic Chemistry*; Research Trends, Council of Scientific Research Integration: India, 1993; Vol. 4, pp 517–534.

(7) Battiste, M. A.; Coxon, J. M. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley and Sons: New York, 1987; Chapter 6.

(8) Skell, P. S.; Day, J. C.; Shea, K. J. *J. Am. Chem. Soc.* **1976**, *98*, 1195.

(9) Lambert, J. B.; Black, R. D. H.; Shaw, J. H.; Papay, J. T. *J. Org. Chem.* **1970**, *35*, 3214. DePuy, C. H. *Fortschr. Chem. Forsch.* **1973**, *40*, 73.

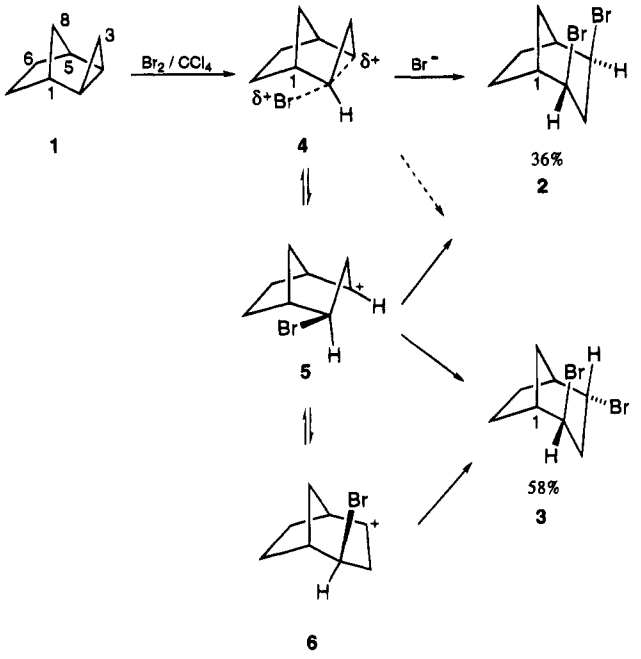
(10) Garratt, D. G. *Can. J. Chem.* **1980**, *58*, 1327.

(11) Lambert, J. B.; Chelius, E. C.; Schulz, W. J., Jr.; Carpenter, N. E. *J. Am. Chem. Soc.* **1990**, *112*, 3156.

(12) CCl_4 is considered a reasonable radical scavenger:

0022-3263/95/1960-2812$09.00/0

Scheme 1. Reaction of *exo*-Tricyclo[3.2.1.0^{2,4}]octane 1 with Bromine



1 4 2 5 3 6

be expected if the reaction were radical in nature.[13] In our study no products containing chlorine were observed, and therefore the reactions were considered to be electrophilic in character.

The reaction of *exo*-tricyclo[3.2.1.0^{2,4}]octane (**1**) with bromine (0.8 mol—to minimize the risk of forming tetrabrominated products) in carbon tetrachloride occurred relatively rapidly at room temperature[14] with only a faint bromine color observable after 3 h. Two major products, 2-*exo*,4-*endo*-dibromobicyclo[3.2.1]octane **3** (58%) and 2-*exo*,4-*exo*-dibromobicyclo[3.2.1]octane **2** (36%), were separated.[15]

The identity of 2-*exo*,4-*exo*-dibromobicyclo[3.2.1]octane (**2**) was determined by X-ray crystal structure analysis. The six-membered ring is flattened as a consequence of carrying two axial bromine substituents but remains in a chair conformation. The ^{13}C NMR spectrum showed only five signals. The ^{1}H−^{1}H connectivity was determined by selective decoupling experiments, and a HETCOR established the one-bond ^{1}H−^{13}C connectivity. A 6.2% enhancement of the multiplet at 1.84 ppm in a difference NOE experiment, on irradiation of the proton centered at 0.80 ppm, confirmed these protons as H3*endo* and H6*endo*/H7*endo*, respectively. The presence of a four bond "*W*" coupling (2.1 Hz) from H6*endo*/H7*endo* to the downfield proton of C8H$_2$ centered at 3.03 ppm established this proton as 8H*syn*. The C8H*anti*, identified from the HETCOR experiment, was centered at 1.10 ppm and exhibited a small coupling (1.5 Hz) to H2 and H4 consistent with the *endo* orientation of these protons and established the bromine substituents as *exo*.[16] The structure of 2-*exo*,4-*endo*-dibromobicyclo[3.2.1]octane (**3**) was determined as follows: a COSY experiment established the ^{1}H−^{1}H connectivity and a heteronuclear correlation experiment (HETCOR) established the ^{1}H−^{13}C one-bond connectivities. The presence of two CHBr groups was determined from the presence of two protons with chemical shifts of 4.24 ppm (H2) and 4.52 ppm (H4) and from the chemical shifts of the associated carbons at 53.0 ppm (C2) and 55.9 ppm (C4). The *exo* stereochemistry of H4 was determined by the presence of a 2.9% NOE to a multiplet centered at 2.30 ppm on irradiation of H4.[17,18] Enhancement of the multiplet at 2.30 ppm (H8*syn*) also established the *syn* orientation of this proton with respect to the largest bridge, and this was confirmed by the absence of a measurable coupling with H1 or H5 consistent with observations for other bicyclo[3.2.1]octane systems.[19] The configuration of bromine at C2 was established as *exo* by the lack of symmetry in the molecule.[20]

For the reaction with bromine the electrophile and nucleophile cannot be distinguished, and hence, comment cannot be made of the trajectory of attack of either the electrophile or the nucleophile in the formation of **3**, although for formation of **2** both electrophile and nucleophile must attack with inversion at C2 and C4. In order to determine the separate trajectories of the electrophile and nucleophile in the formation of **3** the reaction of **1** with bromine was repeated using methanol as the reaction solvent, in which case the methanol can compete with bromide as nucleophile. Reaction of **1** with bromine (0.8 mol equiv) in dry methanol gave four products, 2-*endo*-bromo-5-*endo*-methoxybicyclo[2.2.2]octane (**7**) (50%), 2-*exo*-bromo-4-*exo*-methoxybicyclo[3.2.1]octane (**8**) (46%), 2-*exo*,4-*exo*-dibromobicyclo[3.2.1]octane (**2**) (2%) and a minor product (2%) which was not identified (Scheme 2).

The identity of 2-*exo*-bromo-4-*exo*-methoxybicyclo[3.2.1]-octane (**8**)[21] was established as follows: the similarity in shape of the H2 and H4 multiplets suggested the orientation of these protons to be the same, and comparison with the multiplets of H2 and H4 in **2** suggested them to be *endo*. This was confirmed by the vicinal coupling constants of H2 and H4 to H3*endo*[22] ($^3J_{3endo,2}$ = $^3J_{3endo,4}$ = 5.0 Hz) and the presence of long range couplings, *W*, to H8*anti* ($^4J_{8anti,2}$ = $^4J_{8anti,4}$ = 1.8 Hz).[23] On irradiation of H6*endo* a 4.7% NOE to H4 (2.7% on

(13) The Br−Br bond is weaker than the Cl−C bond of CCl$_4$ and more susceptible to radical attack. Any alkyl radical generated from 1 or 11 would be expected to be sufficiently reactive to react with whatever it collided

(14) Addition of the bromine solution was carried out without absolute exclusion of all light, but subsequent stirring was carried out in the complete absence of light.

(15) A minor product 6% by GLC analysis, was not identified.

(16) Consideration of the chemical shift of H8*syn* (3.03 ppm) is consistent with the assignment of an *exo* orientation of the bromines since this would lead to an expected downfield shift of this proton due to steric compression effects which are also reflected by an upfield shift of C8 (29.8 ppm). Tori, K.; Ueyama, M.; Tsuji, T.; Matsumura, H.; Tanida, H.; Iwamura, H.; Kushida, K.; Nishida, T.; Satoh, S. *Tetrahedron Lett.* **1974**, *32*, 7110. Subramanian, P. M.; Emerson, M. T.; LeBel, N. A. *J. Org. Chem.* **1965**, *30*, 2624.

(17) The reverse NOE was observed but could not be quantified due to the partial overlap of H8*syn* with the multiplet assigned to H3*endo* and H3*exo*. The enhancement of H8*syn* on irradiation of H4 was identified by the multiplicity of this proton (a doublet).

(18) The multiplet at 2.30 ppm had previously been determined from the HETCOR experiment to be a proton attached to C8.

(19) Whittington, B. I. Ph.D. Thesis, University of Canterbury, 1989.

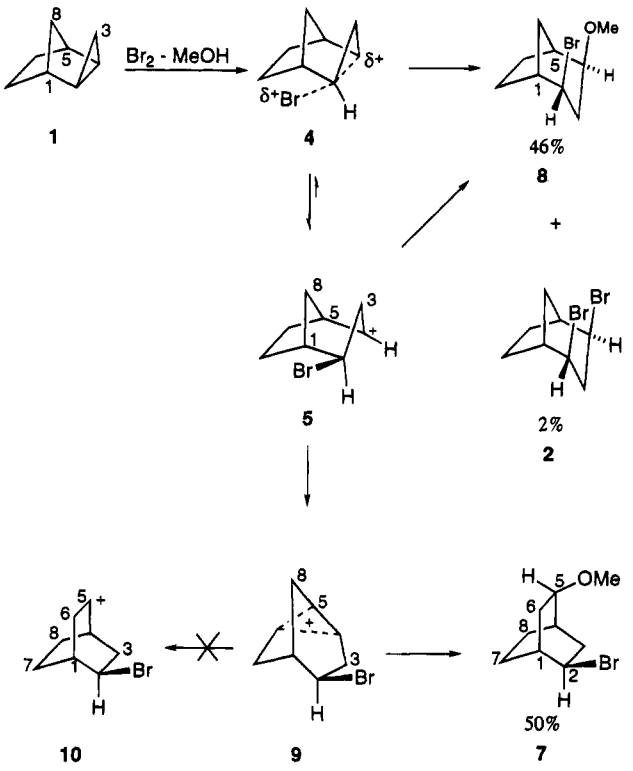
(20) Eight carbon resonances were observed in the ^{13}C spectrum. The presence of a 2.0 Hz coupling in the ^{1}H NMR spectrum from H2 to H8*anti* is consistent with a four bond "*W*" coupling of these protons and hence supports the assigned *endo* orientation of H2.

(21) The ^{1}H−^{1}H and ^{1}H−^{13}C one-bond connectivities were established from COSY and HMQC experiments, respectively. H2 (multiplet 4.21 ppm) and H4 (multiplet 3.26 ppm) were identified as CHBr and CHOMe, respectively, by consideration of their chemical shifts.

(22) The orientation of H3*endo* (d of t centered at 2.05 ppm) was determined by the presence of a 2.5% NOE to this proton on irradiation of the multiplet centred at 1.45 ppm (H7*endo*). On irradiation of H3*endo* a 1.7% NOE to H7*endo* was observed.

(23) Irradiation of H7*endo* gave an NOE (2.7%) to H2 (reverse NOE 1.5% on irradiation of H2) which also supports the assignment of H2 to an *endo* configuration.

Scheme 2. Reaction of *exo*-Tricyclo[3.2.1.0^{2,4}]octane 1 with Bromine in Methanol



reverse irradiation) was observed, consistent with an *endo* orientation of H4. Finally, comparison of the chemical shifts of C8 in **8** and the corresponding carbon in bicyclo[3.2.1]octane[24] (27.9 ppm and 39.7 ppm, respectively) shows a large upfield shift (12 ppm) in **8** consistent with two gauche eclipsed interactions of C8H*syn* with the bromine at C2 and the methoxy of C4, thus confirming the *exo* orientation of the two substituents.

The structure of 2-*endo*-bromo-5-*endo*-methoxybicyclo-[2.2.2]octane (**7**) was established from NMR experiments.[25] Irradiation of the multiplet (1.14−1.23 ppm) corresponding to H7*syn* and H7*anti* gave a 4.8% enhancement of H2 (4.07 ppm) in a difference NOE experiment and established the *exo* orientation of this proton and hence the *endo* orientation of the C2 bromine. The same irradiation showed a 2.8% enhancement of H6*exo* (multiplet centred at 1.72 ppm). Irradiation of the multiplet corresponding to H8*syn* and H8*anti* gave a 2.0% NOE to H5 (multiplet 3.12 ppm) and a 2.0% enhancement of H3*exo* (multiplet 1.91 ppm), thus confirming the *exo* orientation of H5 and, hence, the *endo* orientation of the methoxy group.[26]

Analysis of the products resulting from the bromination of **1** in methanol shows the initial trajectory of the bromine electrophile is from the corner to the C2C4 bond resulting in inversion of configuration at the site of electrophilic attack. It is assumed that the reaction is parallel in CCl_4 and that nucleophilic attack occurs with both retention to give **3** and inversion to give **2**. In CCl_4 rearrangement of C6 to C4 to give the bicyclo[2.2.2]octane skeleton or of C8 to C4 does not compete with nucleophilic attack. Reaction occurs exclusively by 1,3-addition to the C2C4 bond. The stereochemistry at the site of nucleophile attack is such that both retention (**3**) and inversion (**2**) of configuration are observed, with a 1.6:1 preference for retention. This implies the reaction proceeds at least in significant part by way of a "classical" carbocation, **5** or **6** (Scheme 1) and excludes the reaction occurring exclusively by way of an intermediate such as **4**. The intermediacy of **5** and **6** is in agreement with the results of Skell,[8] even though the nonpolar medium will be poor at stabilizing carbocation species. The two dibromides did not undergo interchange in $CDCl_3$, and therefore, the ratio of products in the reaction is considered a kinetic ratio.

In methanol the initially formed cation is trapped with inversion by solvent or bromine to give **8** (46%) and **2** (2%), respectively. In methanol the cation is sufficiently short lived that it does not relax to the classical cation **6** where "equatorial" attack by methanol or bromine with "retention of configuration" can compete; **3** and the methoxy analogue are not formed. In contrast to the reaction in CCl_4 intramolecular capture of the cation by the C5C6 bond with retention to give **9** occurs in competition to the formation of the 1,3-addition product-(s). The Wagner−Meerwein rearrangement and formation of **7** accounts for half of the reaction products. The classical cation **10** can be excluded since this cation would be expected to give both stereoisomers at C5.[27] Nucleophilic attack therefore occurs either to a nonclassical cation **9** or the corresponding rapidly interconverting two classical cations[28] directing nucleophilic attack with inversion at either C4 or C5.

The reaction of *endo*-tricyclo[3.2.1.0^{2,4}]octane (**11**) with bromine (0.8 mol equiv) in carbon tetrachloride gave four products: 2-*endo*,6-*endo*-dibromobicyclo[3.2.1]octane (**12**) (15%), 2-*endo*,4-*endo*-dibromobicyclo[3.2.1]octane (**13**) (29%), 2-*exo*,3-*endo*-dibromobicyclo[3.2.1]octane (**14**) (48%), and a minor product (8%) which was not identified (Scheme 3).[29]

The identity of 2-*exo*,3-*endo*-dibromobicyclo[3.2.1]octane (**14**) was determined from NMR experiments:[30] Irradiation of the multiplet assigned to H6*endo* and H7*endo* gave a small enhancement (1.1%) of H2 in a difference NOE experiment and hence determined H2 as *endo* and therefore requires an *exo* orientation of the bromine attached to C2. The stereochemistry of C3 was estab-

(24) Whitesell, J. K.; Minton, M. A. *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy;* Chapman and Hall: London, 1987.

(25) A COSY experiment gave the proton−proton connectivity; a HETCOR allowed assignment of the one-bond $^1H-^{13}C$ attachments. Carbons C7 and C8 were confirmed as methylene carbons by a DEPT135 experiment.

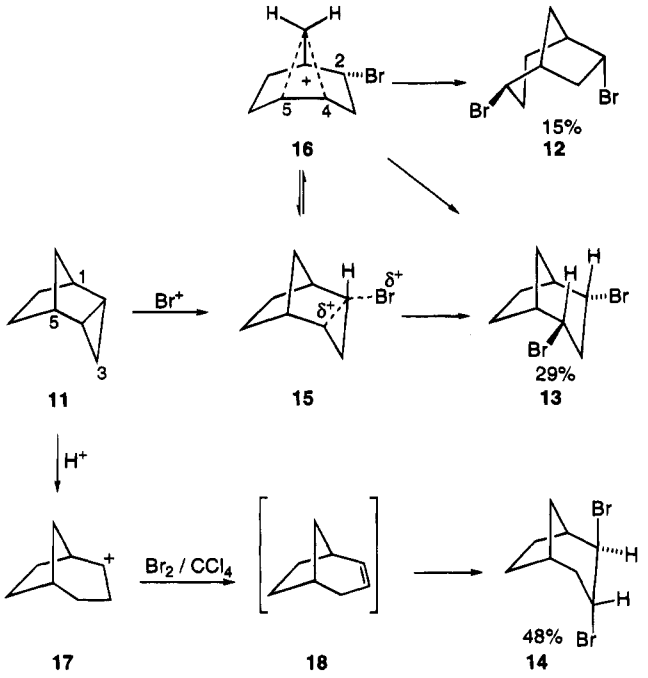
(26) The protons H2 and H5 were identified as being attached to carbons bearing bromine and methoxy substituents, respectively, by consideration of their chemical shifts (4.07 ppm and 3.12 ppm) and from the chemical shifts of the attached carbons (53.2 ppm and 78.1 ppm, respectively), which were determined from the HETCOR experiment. The stereochemical assignments at C5 and C2 were supported by consideration of the coupling constants of H2 and H5 to the protons of the adjacent methylene groups ($^3J_{2,3exo}$ = 10.3 Hz, $^3J_{2,3endo}$ = 6.2 Hz, $^3J_{6exo,5}$ = 9.5 Hz) and from the long range four bond coupling constants ($^4J_{2,6exo}$ = 2.1 Hz, $^4J_{3exo,5}$ = 1.7 Hz) which are consistent with "*W*" couplings from H3*exo* to H5 and H6*exo* to H2.

(27) If the bromine atom of C2 had an effect on the trajectory of nucleophilic attack it would be expected to direct the incoming nucleophile to the opposite side of the cation from both steric and electronic repulsion considerations and, hence, give a different product from that observed.

(28) Brown, H. C. *Acc. Chem. Res.* **1983**, *16*, 432. Dewar, M. J. S.; Merz, K. M., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 5634.

(29) A crude separation was effected by radial chromatography on poly(ethylene glycol) (PEG, MW = 6000 g mol^{-1}) coated silica. Compound **14** was further purified by preparative gas liquid chromatography. The other major products **12** and **13** were separated by preparative TLC (multiple elution, 3% ethyl acetate/pentane, silica).

Scheme 3. Reaction of *endo*-Tricyclo[3.2.1.0^{2,4}]octane (11) with Bromine



lished from the coupling constant of H3 to H4*exo* ($^3J_{3,4exo}$ = 6.2 Hz, $^3J_{4exo,3}$ = 6.4 Hz) and the absence of measurable coupling to H4*endo*, (no large *trans* coupling). The coupling constants of H4*exo* and H4*endo* to H5 ($^3J_{4exo,5}$ = 3.2 Hz, $^3J_{4endo,5}$ = 3.4 Hz), and absence of a *trans* coupling to H3 confirmed the *exo* orientation of H3 and the *endo* orientation of the C3 bromine.[31]

The ^{13}C NMR spectrum of 2-*endo*-4-*endo*-dibromobicyclo-[3.2.1]octane (**13**)[32] showed five peaks and hence the symmetry in the molecule. 2D-NMR experiments identified the bicyclo[3.2.1]octane skeleton and C2 and C4 to be substituted with bromine (53.2 ppm). Since structure **2** could be excluded (known from the bromination of **1**), the only possible structure, **13**, had an *endo* orientation of the bromines. This assignment was confirmed by the presence of a 2.3% enhancement of H2/H4 upon irradiation of H8*syn* (doublet 1.55 ppm) in a difference NOE experiment (1.6% enhancement of H8*syn* was observed on irradiation of H2/H4).[33] The structure of 2-*endo*-6-*endo*-dibromobicyclo[3.2.1]octane (**12**) was elucidated from NMR experiments.[34] The orientation of H2 was confirmed by the presence of a 1.5% enhancement of the proton assigned to H8*syn* (1.65 ppm) on irradiation of H2 in a difference NOE experiment.[35] The *exo* orientation of H6 was confirmed by NOE experiments which showed a 1.8% enhancement of H6 on irradiation of H8*anti* (1.77 ppm).

The formation of the 1,2-dibromide **14** was unusual and could arise by addition to an intermediate alkene formed by catalytic amounts of HBr formed in the reaction mixture.[36] Bromination of cyclopropanes occurs slowly in comparison with the acid-promoted ring cleavage.[37] Our attempts to isolate the intermediate alkene by reaction with catalytic amounts of acid failed. Alternatively, **14** could be formed by bromine attack to the cyclopropane ring with retention followed by hydride migration and nucleophilic attack. In no other product is electrophilic attack with retention observed, and we consider this mechanism unlikely. In methanol neither the dibromide **14** nor the methoxy analogue is observed. To investigate the mechanism of formation of **13** and **12** the addition was repeated but with methanol as solvent. Reaction of **11** with bromine (0.9 mol equiv) in dry methanol gave three products: 2-*endo*-bromo-4-*endo*-methoxybicyclo[3.2.1]octane (**19**) (53%), 6-*endo*-bromo-2-*endo*-methoxybicyclo[3.2.1]octane (**20**) (44%), and 2-*endo*, 4-*endo*-dibromobicyclo[3.2.1]octane (**13**)(Scheme 4).

The identification of 2-*endo*-bromo-4-*endo*-methoxybicyclo[3.2.1]octane (**19**) was hampered by only six protons (including three of the methoxy group) being clearly differentiated in the ^{1}H NMR spectrum when run in $CDCl_3$ making determination of the ^{1}H–^{1}H connectivity and even the ^{1}H–^{13}C one-bond connectivity difficult.[38] A 2D-TOCSY experiment established the 1,3 relationship of the CHBr and CHOMe protons (H2 and H4, respectively), identified from their chemical shifts, 4.12 ppm and 3.17 ppm, respectively. A 1D-TOCSY performed by irradiation of H2 permitted determination of the chemical shift and multiplicity of H3*endo* (d of t, 1.69 ppm) and the coupling constants of this proton to H3*exo*, H4, and H2 to be calculated ($^2J_{3endo,3exo}$ = 13.0 Hz, $^3J_{3endo,2}$ = $^3J_{3endo,4}$ = 10.9 Hz). Analysis of the coupling constants calculated from this proton and from H2 ($^3J_{2,3endo}$ = 11.3 Hz, $^3J_{2,3exo}$ = 5.4 Hz) and H4 ($^3J_{4,3endo}$ = 12.2 Hz, $^3J_{4,3exo}$ = 5.2 Hz) confirmed the assignment of the proton at 1.69 ppm as H3*endo* and the size of the coupling constants from H2 and H4 to H3*endo* (ca. 11 Hz) showed a *trans* relationship of these protons.[39] A DEPT135 experiment established the carbon resonance at 37.1 ppm to be a methine carbon

(30) A double quantum filtered COSY (DQCOSY) experiment in conjunction with proton decoupling experiments established the ^{1}H–^{1}H connectivity and an HMQC experiment established the one-bond ^{1}H–^{13}C connectivity. The DQCOSY showed a strong coupling of H1 (2.64 ppm) and H5 (2.34 ppm) to the multiplets centered at 1.85 and 1.77 ppm, respectively, establishing these two protons as H7*exo* and H6*exo*, respectively. From the DQCOSY and HMQC experiments the multiplet at 2.19–2.29 ppm was assigned to H6*endo* and H7*endo*.

(31) The chemical shifts of H8*syn*, H6*endo*, and H7*endo* all show significant downfield shifts which are also consistent with the proposed stereochemistry at both C2 and C3.

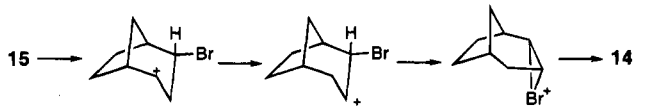
(32) Analysis of a DQCOSY and HMQC experiment established the ^{1}H–^{1}H connectivity and ^{1}H–^{13}C one-bond connectivity, respectively.

(33) The *syn* orientation of the doublet centered at 1.55 ppm was confirmed by the presence of only a small coupling to H1 and H5, whereas H8*anti* showed a 5.3 Hz coupling to both H1 and H5 which is diagnostic in bicyclo[3.2.1]octane compounds.[19]

(34) As far as was possible a DQCOSY experiment established the ^{1}H–^{1}H connectivity. The ^{1}H–^{13}C one-bond connectivities were established from HMQC and HMQC–DEPT experiments. The presence of a bicyclo[3.2.1]octane structure was determined from HMBC and HMQC–TOCSY experiments which also allowed the assignment of C4 and C3 at 30.4 ppm and 30.9 ppm, respectively, from a correlation of H6 to C4 in the HMBC experiment and a correlation from H2 to C3 observed in the HMQC–TOCSY experiment when the spectrum was acquired using a short mixing time (ca. 10 ms).

(35) The reverse NOE could not be measured due to the partial overlap of H8*syn* and H4*exo*, both of which would be expected to give enhancements of H2 on irradiation of this multiplet in a difference NOEexperiment.

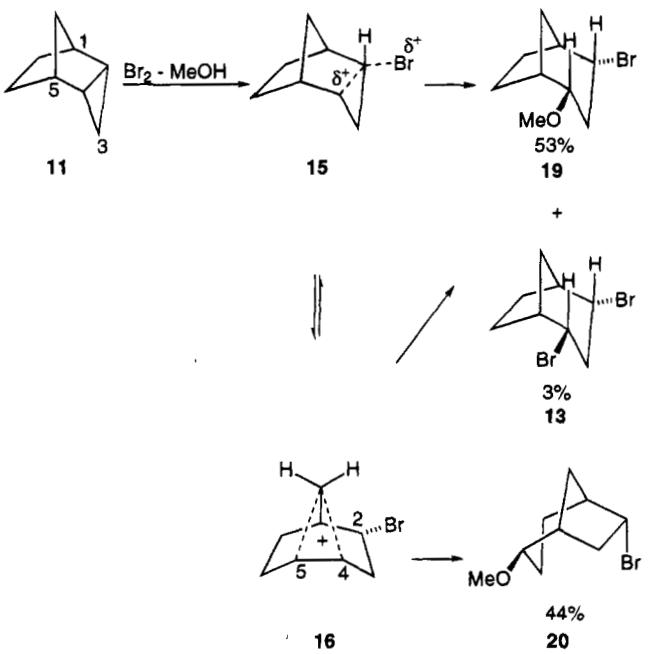
(36) We thank a reviewer for the suggestion that **14** could be formed by initial bromine attack at C2 followed by migration of C3H to C2, bromonium ion fomation followed by bromide attack at C2.



(37) Attempts to test the mechanism of formation of **14** by reaction of **1** with traces of trifluoroacetic acid (TFA–CCl_4) and HBr–acetic acid in CCl4 at room temperature and 70 °C failed to give any observable (1H NMR) formation of **18**.

(38) A DQCOSY experiment gave little structural information due the partial overlap of H1, H3*exo*, and H5 as a multiplet at 2.41–2.48 ppm in the proton NMR spectrum.

Scheme 4. Reaction of *endo*-Tricyclo[3.2.1.0^{2,4}]octane (11) with Bromine in Methanol



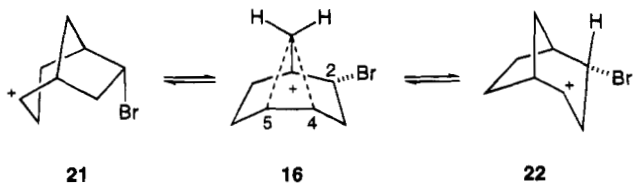
and the carbon at 37.0 ppm to be a methylene carbon.[40] After the one-bond $^1H-^{13}C$ was established an HMBC experiment was used to obtain long range $^1H-^{13}C$ correlations (two- and three-bond $^1H-^{13}C$ couplings). The doublet at 1.33 ppm, which was shown (HMQC) to be part of a methylene group, showed correlations to four carbons. Two of these carbons were methylene carbons and the other two were the CHBr and CHOMe carbons which had previously been determined to have a 1,3 relationship. This established the general bicyclo[3.2.1]octane carbon skeleton.[41] The stereochemistry of C2 and C4 was assigned by the following: the DQCOSY, and the correlations to the doublet at 1.33 ppm in the HMBC, established this proton to be one of the C8 methylene group protons. A 1D-TOCSY on this proton showed a correlation to the second proton of the C8 methylene group (d of t centered at 1.71 ppm). From this experiment the coupling constants of the proton centered at 1.71 ppm (H8*anti*) to H1 and H5 could be extracted ($^3J_{8anti,1} = {}^3J_{8anti,5} = 5.9$ Hz). This therefore established the proton at 1.71 ppm as H8*anti*[19] and the doublet at 1.33 ppm as H8*syn*. A difference NOE experiment showed a 3.2% enhancement of H2 and a 1.7% enhancement of H4 on irradiation of H8*syn* (2.2% and 1.9%, respectively, in the reverse irradiations). This establishes the orientation of both H2 and H4 as *exo* and the orientation of the bromine attached to C2 and the methoxy attached to C4 (identified from their chemical shifts of 53.8 ppm and 80.5 ppm, respectively, and from the HMQC experiment) as being *endo*.

(39) The $^1H-^{13}C$ one-bond connectivity was determined by an HMQC experiment. However, the experiment was not performed at high enough resolution to distinguish the proton correlations to the carbons at 37.1 and 37.0 ppm and was also complicated by both carbons correlating to the multiplet at 2.41−2.48 ppm.

(40) The use of an HMQC−DEPT experiment enabled the resolution of the proton correlations as CH and methylene groups show correlations with a "positive" and "negative" phase, respectively.

(41) No other carbon skeleton with the given number of methine and methylene carbons could account for the observed two- and three-bond correlations to the proton at 1.33 ppm in the HMBC experiment.

Scheme 5. Interconversion of Clasical Cations 21 and 22



The identity of 6-*endo*-bromo-2-*endo*-methoxybicyclo-[3.2.1]octane (**20**) was determined as follows:[42] An HMBC experiment confirmed the general bicyclo[3.2.1]octane carbon skeleton.[43] The *exo* orientation of H2 was determined from the presence of a 1.2% enhancement of H8*syn* (1.44 ppm) on irradiation of H2 in a difference NOE experiment (1.6% enhancement was observed for the reverse irradiation).[44] This establishes an *endo* orientation of the methoxy group attached to C2. Irradiation of H8*anti* (1.70 ppm, established from an HMQC experiment as geminal to the multiplet at 1.44 ppm (H8*syn*) gave a 1.6% enhancement of H6 in a difference NOE experiment and hence determined this proton to have an *exo* orientation.[45]

Analysis of the products obtained from bromination of **11** in methanol shows that bromine attack occurred exclusively to the corner of the C2C4 bond. From a comparison of the products from reaction in methanol with those in CCl_4 it is assumed that the addition of bromine in CCl_4 also occurs by the electrophile attacking at the corner of the cyclopropane ring. Nucleophilic addition in methanol occurred with inversion of configuration to give **19** and **20**. These products are analogous to those formed in CCl_4, and therefore, it is assumed that they arise in a similar manner in that solvent. The absence of products resulting from nucleophilic capture of the cation with retention of configuration would suggest that nucleophilic attack occurs before the structure has relaxed to an open cation.

When the reaction was performed in CCl_4 the rearrangement product **12** was formed in approximately a 1:2 ratio with the product **13** resulting from nucleophilic capture of the carbocation before rearrangement can occur. The predominance of products resulting from nucleophilic capture before rearrangement would therefore suggest that a corner-brominated intermediate **15** is formed similar to that suggested by Coxon et al.[5a,d] for the protonation and mercuration of **11**. Alternatively the cation **16** is unsymmetrical with a higher amount of positive charge at C4 than at C5 or the equilibrating classical cations **22** and **21** are heavily biased to **22** (Scheme 5) by inductive effect of the bromine at C2.

For the reaction in methanol a larger proportion of the reaction involves rearrangement to **20** than to **12** observed in CCl_4 (1.0:1.2[46]) and may reflect stabilization of the rearrangement process by the more polar solvent.

(42) A HMQC experiment established the one-bond $^1H-^{13}C$ connectivity, and a DQCOSY established the proton−proton connectivity.

(43) The chemical shift of C2 at 80.8 ppm established this carbon as being attached to a methoxy group, and this was reflected in the chemical shift of H2 at 3.24 ppm. The methoxy CH_3 signal was clearly evident as a singlet ($W_{h/2} = 0.6$ Hz) at 3.30 ppm in the ^1H NMR spectrum and showed a ^{13}C resonance at 55.4 ppm. The proton signal of the CHBr group was evident at 4.36 ppm and the corresponding carbon signal C6 at 52.5 ppm.

(44) This assignment was supported by a 10.3 Hz coupling constant to H3*endo* (1.51 ppm) and a 3.4 Hz coupling to both H3*exo* and H1.

(45) This was confirmed by consideration of the coupling constants of H6 to H7*exo* ($^3J_{6,7exo} = 10.7$ Hz) and H7*endo* ($^3J_{6,7endo} = 5.7$ Hz).

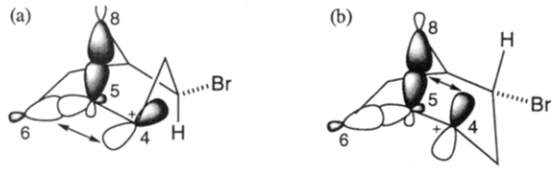


Figure 1. Cations resulting from ring oening of (a) *exo*-tricyclo[3.2.1.0^{2,4}]octane (**1**) and (b) *endo*-tricyclo[3.2.1.0^{2,4}]-octane (**11**) on reaction with bromine showing the favorable orbital interactions.

A similar increase in the importance of skeletal rearrangement was observed in bromination of **1** in methanol as compared with CCl_4.

Reactions of *exo*-**1** and *endo*-**11** hydrocarbons with bromine in CCl_4 and methanol are initiated by attack at the corner of the cyclopropane ring followed by rupture of the C2C4 bond. This parallels the corresponding reactions with proton acid and is contrary to what would be predicted by Markovnikov's rule as stated for cyclopropane opening. Reactions of **1** and **11** follow different paths after attack by the electrophile and ring opening. The *exo*-hydrocarbon **1** undergoes a Wagner−Meerwein rearrangement of C6 to C2 with formation of a bicyclo-[2.2.2]octane structure. The *endo*-hydrocarbon **11** undergoes a 1,2 methylene migration of C8 from C1 to C2 and gives products containing the bicyclo[3.2.1]octane skeleton. This suggests that the secondary cation at C4 that would be formed by electrophilic attack at C2 and rupture of the C2C4 bond is sufficiently high in energy to require the involvement of an aligned and proximate σ-CC bond: C5C6 for **1** and C5C8 for **11.**

Simple molecular mechanics[47] calculations show a difference in ring geometry between the classical cations resulting from cyclopropane ring opening of **11** and **1**. The carbocation formed on cyclopropane ring opening of **1** (Figure 1a) allows for interaction of the vacant C4 *p* orbital with the C5−C6 bond favoring Wagner−Meerwein rearrangement to the bicyclo[2.2.2]octane skeleton as observed. For **11**, the classical carbocation resulting from cyclopropane ring opening (Figure 1b) has the vacant *p* orbital of C4 aligned with the C5−C8 bond rather than the C5−C6 allowing for rearrangement involving migration of the C5−C8 bond with retention and formation of the bicyclo[3.2.1]octane skeleton.

Conclusion

The results of the studies of bromination of **1** and **11** show reaction occurs preferentially at the most substituted (C2−C4) cyclopropyl bond with inversion of configuration at the site of electrophilic attack. Reaction of **1** with bromine in CCl_4 gives 1,3-addition products by electrophilic attack with inversion at the corner to the C2C4 bond and nucleophilic attack by both inversion and retention showing the reaction proceeds at least in part by way of a classical ion. In methanol the cation species formed by bromine attack at the corner of the C2C4 bond with inversion is sufficiently short lived that it does not relax to the classical cation and nucleophilic attack only with inversion competes with skeletal rearrangement to give **7**. The cation precursor to **7** does not relax to the classical cation **10.** Reaction of **11** with bromine in CCl_4 gives 1,3-addition and addition rearrangement to **12** with inversion at the site of electrophilic and nucleophilic attack. The cation intermediates are formed in the more stable chair conformation (cf. **1** where at least in part the boat cation relaxes to the chair) but such that no nucleophilic attack occurs from the "top face" the nucleophile reacting exclusively with inversion. The dibromide **14** was unexpected and its formation is suppressed in methanol. In methanol nucleophile attack occurs with inversion. These studies demonstrate that addition of bromine, proton acids, and mercuric acetate to these tricyclic hydrocarbons have considerable similarity. The reactions occur by rupture of the more substituted cyclopropane bond, and inversion of configuration at the site of electrophilic attack dictates the dominant trajectory for the electrophile. These results contrast with Lambert's study[11] of the reaction of deuterated cyclopropane with bromine where the electrophile would "appear to attack cyclopropane at the edge with retention."

Experimental Section

NMR spectra were recorded on Varian XL-300 or Varian Unity 300 spectrometers equipped with a 5 mm probe and operating at 300 and 75 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts are reported in ppm relative to tetramethylsilane. Difference NOE spectra were obtained in arrayed experiments with the decoupler offset 10 000 Hz and then cycled with low power over the multiplet peaks of the desired proton for irradiation, a procedure based on that of Kinns and Sanders.[48] All other NMR experiments were recorded using standard pulse sequences and parameters available with the XL-300 or Unity 300 systems. Proton chemical shifts marked with a superscript asterisk were estimated from NOE or two-dimensional NMR experiments (COSY, DQCOSY, HETCOR, or HMQC experiments). Proton chemical shifts marked with a superscript hash mark (#) were determined from 1D- or 2D-TOCSY experiments. Infrared spectra were recorded on a Perkin-Elmer 1600 Series FT-IR spectrometer. Mass spectra were recorded by GCMS using a Kratos MS80RFA spectrometer directly coupled to a Carlo Erba 500 Series GLC fitted with a Restex R_{tx}1 30 m × 0.32 mm capillary column. A programmed run was used for the GCMS (an initial temperature of 60 °C was held for 1 min and then the column temperature increased at the rate of 20 °C per minute up to 260 °C) to ensure that the sample and all impurities passed through the column to the MS instrument. In some cases molecular ion peaks were not observed in the high-resolution mass spectra (HRMS) but were identified in the low-resolution spectra (LRMS); in these cases the LRMS and HRMS spectra are shown along with a number of fragment ion peaks which were observed. A Hewlett-Packard HP5890A GLC was used in both analytical and preparative modes with either a 1.5% OV-17, 1.25% QF-1 chromosorb W packed column of 5 mm external diameter and 3.0 m length or a 1.5% OV-17, 1.95% QF-1 chromosorb W packed column of 10 mm external diameter and 2.5 m length. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. Radial chromatography was performed on a chromatotron (Harrison and Harrison) using Merck grade 60PF$_{254}$ silica gel or poly(ethylene glycol) (PEG, molecular weight 6000 g mol^{-1})-coated silica plates. TLC mesh column chromatography[49] was performed on Merck 60PF$_{254+366}$ grade silica gel. *endo*-Tricyclo[3.2.1.0^{2,4}]oct-6-ene,[50] *exo*-tricyclo[3.2.1.0^{2,4}]-octane[5a,51,52] (**1**), and *endo*-tricyclo[3.2.1.0^{2,4}]octane[5a,53] (**11**) were prepared according to literature procedures.

(46) This ratio includes the products resulting from methanol capture only and does not include the small amount of **13** isolated in this reaction, as a similar amount of **12** may also have been present but not isolated.

(47) Using PCMODEL with an MMX force field.

(48) Kinns, M.; Sanders, J. K. M. *J. Magn. Reson.* **1984**, *56*, 518.
(49) Taber, D. F. *J. Org. Chem.* **1982**, *47*, 1351.
(50) Closs, G. L.; Krantz, K. D. *J. Org. Chem.* **1966**, *31*, 638.
(51) Rawson, R. J.; Harrison, I. T. *J. Org. Chem.* **1970**, *35*, 2057.

Reaction of *exo*-Tricyclo[3.2.1.0^{2,4}]octane 1 with Bromine in Carbon Tetrachloride. Bromine (371 mg, 2.32 mmol) in CCl_4 (10 mL) was added dropwise over 10 min to a stirred solution of **1** (313 mg, 2.89 mmol, 1.1 mol equiv) in CCl_4 (5 mL). The reaction was stirred in the dark at room temperature for 3 h after which time it was washed with an aqueous sodium metabisulfite solution and twice with water. The CCl_4 was separated, dried over $MgSO_4$, and carefully removed under reduced pressure to give a yellow oil (491 mg, ca. 79% recovery). GLC analysis showed the presence of three products, 2-*exo*-4-*endo*-dibromobicyclo[3.2.1]octane (**3**) (58%), 2-*exo*-4-*exo*-dibromobicyclo[3.2.1]octane (**2**) (36%), and one other compound (ca. 6%) which was not identified. The major products were separated by column chromatography (silica gel, 67:1 ratio absorbant to sample loaded, pentane elution). **2-*exo*,4-*endo*-Dibromobicyclo[3.2.1]octane** (**3**) was obtained as a colorless oil. ^{1}H NMR δ_H ($CDCl_3$): 4.52 (m, $^3J_{4,3endo}$ = 11.1 Hz, $^3J_{4,3exo}$ = 5.8 Hz, $^4J_{4,6exo}$ = 1.0 Hz, H4), 4.24 (m, $^4J_{2,8anti}$ = 2.0 Hz, H2), 2.57* (H5), 2.53* (H1), 2.33−2.45 (m, H3*endo*, H3*exo*), 2.30 (d, $^2J_{8syn,8anti}$ = 12.5 Hz, H8*syn*), 1.87 (m, $^4J_{6endo,8syn}$ =2.1 Hz, H6*endo*), 1.82* (H7*exo*), 1.71 (m, H6*exo*), 1.58 (m, $^2J_{8anti,8syn}$ = 12.5 Hz, $^3J_{8anti,1}$ = $^3J_{8anti,5}$ = 5.0 Hz, $^4J_{8anti,2}$ = 2.0 Hz, H8*anti*), 1.47 (m, $^4J_{7endo,8syn}$ = 2.0 Hz, H7*endo*). ^{13}C NMR δ_C ($CDCl_3$): 55.9 (C4), 53.0 (C2), 44.1 (C5), 42.1 (C1), 39.7 (C3), 35.2 (C8), 28.8 (C7), 23.8 (C6). HRMS: $C_8H_{12}{}^{81}Br_2$ M$^{\bullet+}$ requires 269.9267, found 269.9180 (2.6), $C_8H_{12}{}^{79}Br\ {}^{81}Br$ M$^{\bullet+}$ requires 267.9287, found 267.9235 (7.0); $C_8H_{12}{}^{79}Br_2$ M$^{\bullet+}$ requires 265.9307, found 265.9240 (4.6); $C_8H_{11}{}^{81}Br_2$ [M − 1]$^+$ requires 268.9189, found 268.9187 (36.0); $C_8H_{11}{}^{79}Br{}^{81}Br$ [M − 1]$^+$ requires 266.9209, found 266.9208 (78.8); $C_8H_{11}{}^{79}Br_2$ [M − 1]$^+$ requires 264.9229, found 264.9231 (41.9). **2-*exo*,4-*exo*-Dibromobicyclo[3.2.1]octane** (**2**) was obtained as colourless crystals from CCl_4. Mp: 109−111 °C. ^{1}H NMR δ_H (C_6D_6): 3.77 (m, H2, H4), 3.03 (d, $^2J_{8syn,8anti}$ = 12.4 Hz, H8*syn*), 2.31 (m, H1, H5), 2.18 (d, $^2J_{3exo,3endo}$ = 17.7 Hz, H3*exo*), 1.84 (d of t, $^2J_{3endo,3exo}$ = 17.8 Hz, $^3J_{3endo,2}$ = $^3J_{3endo,4}$ = 5.5 Hz, H3*endo*), 1.29 (m, H6*exo*, H7*exo*), 1.10 (m, $^2J_{8anti,8syn}$ = 12.4 Hz, $^3J_{8anti,1}$ = $^3J_{8anti,5}$ = 5.6 Hz, $^4J_{8anti,2}$ = $^4J_{8anti,4}$ = 1.5 Hz, H8*anti*), 0.80 (m, $^2J_{6endo,6exo}$ = $^2J_{7endo,7exo}$ = 15.6 Hz, $^4J_{6endo,8syn}$ = $^4J_{7endo,8syn}$ = 2.1 Hz, H6*endo*, H7*endo*). ^{13}C NMR δ_C (C_6D_6): 52.1 (C2, C4), 44.0 (C1, C5), 35.5 (C3), 29.8 (C8), 28.7 (C6, C7). IR (KBr): 2958 (m), 2620 (m), 1653 (m), 1628 (m) cm^{-1}. HRMS: $C_8H_{12}{}^{81}Br_2$ M$^{\bullet+}$ requires 269.9267, found 269.9288 (2.6); , $C_8H_{12}{}^{79}Br\ {}^{81}Br$ M$^{\bullet+}$ requires 267.9287, found 267.9295 (5.5); $C_8H_{12}{}^{79}Br_2$ M$^{\bullet+}$ requires 265.9307, found 265.9311 (3.1).

Reaction of *exo*-Tricyclo[3.2.1.0^{2,4}]octane (1) with Bromine in Methanol. Bromine (348 mg, 2.18 mmol) in dry methanol (10 mL) was added dropwise over 10 min to a stirred solution of **1** (296 mg, 2.74 mmol, 1.26 mol equiv) in dry methanol (5 mL) at room temperature. The reaction was stirred in the dark for 1.5 h after which time it was diluted with an aqueous solution of sodium metabisulfite (15 mL) and extracted with ether (2 × 20 mL). The ether extracts were combined, washed with saturated brine solution (5 mL), and dried over $MgSO_4$ and the solvent removed under reduced pressure to give a yellow oil (355 mg, ca. 74% recovery). GLC analysis showed the presence of four products, 2-*endo*-bromo-5-*endo*-methoxybicyclo[2.2.2]octane (**7**) (50%), 2-*exo*-bromo-4-*exo*-methoxybicyclo[3.2.1]octane (**8**) (46%), 2-*exo*,4-*exo*-dibromobicyclo[3.2.1]octane (**2**) (2%), and one other compound (2%) which was not identified. A crude separation was effected by radial chromatography (2 mm silica plate, gradient elution starting with 2% ether/pentane) after which the major products were further purified by column chromatography (silica gel, 100:1 ratio absorbant to sample, 2% ether/petroleum ether elution). 2-*exo*,4-*exo*-Dibromobicyclo[3.2.1]octane (**2**) was identified by comparison of its ^{1}H NMR data with that reported above for the reaction of **1** with bromine in CCl_4. **2-*endo*-Bromo-5-*endo*-methoxybicyclo[2.2.2]octane** (**7**) was obtained as a colourless oil. ^{1}H NMR δ_H (C_6D_6): 4.07 (m, $^3J_{2,1}$ = 2.1 Hz, $^3J_{2,3endo}$ = 6.2 Hz, $^3J_{2,3exo}$ = 10.3 Hz, $^4J_{2,6exo}$ = 2.1 Hz, H2), 3.16 (s, $W_{h/2}$ = 0.8 Hz, OMe), 3.12 (m, H5), 2.62 (d of d, $^2J_{3endo,3exo}$ = 14.4 Hz, $^3J_{3endo,2}$ = 6.2 Hz, H3*endo*), 2.24 (m, $^2J_{6endo,6exo}$ = 14.1 Hz, H6*endo*), 1.91 (m, $^2J_{3exo,3endo}$ = 14.2 Hz, $^3J_{3exo,2}$ = 10.3 Hz, $^3J_{3exo,4}$ = 3.9 Hz, $^4J_{3exo,5}$ = 1.7 Hz, H3*exo*), 1.83 (m, H1), 1.72 (m, $^2J_{6exo,6endo}$ = 13.5 Hz, $^3J_{6exo,5}$ = 9.5 Hz, $^3J_{6exo,1}$ = 4.1 Hz, $^4J_{6exo,2}$ = 2.0 Hz, H6*exo*), 1.55 (m, H4) 1.14−1.23 (m, H7*anti*, H7*syn*), 1.04−1.13 (m, H8*anti*, H8*syn*). ^{13}C NMR δ_C (C_6D_6): 78.1 (C5), 55.8 (OMe), 53.2 (C2), 35.1 (C1), 33.2 (C3), 30.5 (C4), 30.2 (C6), 25.6 (C7), 22.1 (C8). LRMS: $C_9H_{15}{}^{81}BrO$ M$^{\bullet+}$ requires 220, found 220 (85); $C_9H_{15}{}^{79}BrO$ M$^{\bullet+}$ requires 218, found 218 (84). HRMS: $C_9H_{15}{}^{79}BrO$ M$^{\bullet+}$ requires 218.0307, found 218.0300 (3.6). **2-*exo*-Bromo-4-*exo*-methoxybicyclo[3.2.1]octane** (**8**) was obtained as a colourless oil. ^{1}H NMR δ_H ($CDCl_3$): 4.21 (m, H2), 3.34 (s, $W_{h/2}$ = 0.7 Hz, OMe), 3.26 (m, H4), 2.53 (d, $^2J_{8syn,8anti}$ = 12.0 Hz, H8*syn*), 2.50* (H1), 2.45 (m, H5), 2.21 (d, $^2J_{3exo,3endo}$ = 16.5 Hz, H3*exo*), 2.05 (d of t, $^2J_{3endo,3exo}$ = 16.5 Hz, $^3J_{3endo,2}$ = $^3J_{3endo,4}$ = 5.0 Hz, H3*endo*), 1.75−1.80 (m, H6*exo*, H7*exo*), 1.45 (m, $^4J_{7endo,8syn}$ = 1.8 Hz, H7*endo*), 1.34 (m, $^4J_{6endo,8syn}$ = 1.8 Hz, H6*endo*), 1.22 (m, $^2J_{8anti,8syn}$ = 12.0 Hz, $^3J_{8anti,1}$ = $^3J_{8anti,5}$ = 4.7 Hz, $^4J_{8anti,2}$ = $^4J_{8anti,4}$ = 1.8 Hz, H8*anti*). ^{13}C NMR δ_C ($CDCl_3$): 79.7 (C4), 56.0 (OMe), 53.7 (C2), 43.3 (C1), 38.0 (C5), 30.6 (C3), 28.1 (C7), 27.9 (C8), 25.9 (C6). HRMS: $C_9H_{15}{}^{81}BrO$ M$^{\bullet+}$ requires 220.0287, found 220.0279 (16.4); $C_9H_{15}{}^{79}BrO$ M$^{\bullet+}$ requires 218.0307, found 218.0297 (16.8).

Reaction of *endo*-Tricyclo[3.2.1.0^{2,4}]octane (11) with Bromine in Carbon tetrachloride. To stirred solution of **11** (150 mg, 1.39 mmol) in CCl_4 (2 mL) was added bromine (186 mg, 1.16 mmol, 0.83 mol equiv) in CCl_4 (5 mL) dropwise over 10 min. The reaction was stirred in the absence of light for 4 h and then washed with a solution of sodium metabisulfite and water (5 mL) and dried over $MgSO_4$. The solvent was carefully removed under reduced pressure to give a yellow oil (268 mg, ca. 86% recovery) which was shown by GLC analysis to consist of four compounds, 2-*exo*,3-*endo*-dibromobicyclo[3.2.1]octane (**14**) (48%), 2-*endo*,4-*endo*-dibromobicyclo-[3.2.1]octane (**13**) (29%), 2-*endo*,6-*endo*-dibromobicyclo[3.2.1]-octane (**12**) (15%), and one other compound (8%) which was not identified. A crude separation of the products was effected by radial chromatography (1 mm PEG coated silica plate, pentane elution). 2-*exo*,3-*endo*-Dibromobicyclo[3.2.1]octane (**14**) was further purified by preparative GLC. Compounds **13** and **12** were separated by preparative TLC (analytical grade silica TLC plates, multiple elution with 3% ethyl acetate/pentane). **2-*exo*,3-*endo*-Dibromobicyclo[3.2.1]octane** (**14**) was obtained as a colorless oil. ^{1}H NMR δ_H ($CDCl_3$): 4.84 (s, $W_{h/2}$ = 6.9 Hz, H2), 4.66 (d, $^3J_{3,4exo}$ = 6.3 Hz, H3), 2.64 (m, H1), 2.51 (m, $^2J_{4exo,4endo}$ = 15.9 Hz, $^3J_{4exo,3}$ = 6.4 Hz, $^3J_{4exo,5}$ = 3.2 Hz, H4*exo*), 2.34 (m, H5), 2.19−2.29 (m, H6*endo*, H7*endo*), 2.10 (m, $^2J_{4endo,4exo}$ = 15.7 Hz, $^3J_{4endo,5}$ = 3.4 Hz, H4*endo*), 2.06 (d, $^2J_{8syn,8anti}$ = 11.7 Hz, H8*syn*), 1.85* (H7*exo*), 1.77* (H6*exo*), 1.44 (m, H8*anti*). ^{13}C NMR δ_C ($CDCl_3$): 60.1 (C2), 48.8 (C3), 43.6 (C1), 36.7 (C4), 33.9 (C5), 33.1 (C8), 29.1 (C7), 27.4 (C6). LRMS: $C_8H_{12}{}^{81}Br_2$ M$^{\bullet+}$ requires 270, found 270 (0.3); $C_8H_{12}{}^{79}Br{}^{81}Br$ M$^{\bullet+}$ requires 268, found 268 (0.5); $C_8H_{12}{}^{79}Br_2$ M$^{\bullet+}$ requires 266, found 266 (0.3); $C_8H_{12}{}^{81}Br$ [M − Br]$^+$ requires 189, found 189 (66); $C_8H_{12}{}^{79}Br$ [M − Br]$^+$ requires 187, found 187 (67). HRMS: $C_8H_{12}{}^{79}Br{}^{81}Br$ M$^{\bullet+}$ requires 267.9287, found 267.9249 (1.3); $C_8H_{12}{}^{81}Br$ [M − Br]$^+$ requires 189.0103, found 189.0097 (100.0); $C_8H_{10}{}^{79}Br$ [M − 83]$^+$ requires 184.9966, found 184.9949 (2.1). **2-*endo*,4-*endo*-Dibromobicyclo[3.2.1]-octane** (**13**) was obtained as a colorless oil. ^{1}H NMR δ_H ($CDCl_3$): 4.09 (m, $^3J_{2,1}$ = $^3J_{4,5}$ = 2.8 Hz, $^3J_{2,3endo}$ = $^3J_{4,3endo}$ = 11.8 Hz, $^3J_{2,3exo}$ = $^3J_{4,3exo}$ = 5.2 Hz, H2, H4), 2.64 (m, $^2J_{3exo,3endo}$ = 13.4 Hz, $^3J_{3exo,2}$ = $^3J_{3exo,4}$ = 5.3 Hz, H3*exo*), 2.55 (m, H1, H5), 2.24 (d of t, $^2J_{3endo,3exo}$ = 13.3 Hz, $^3J_{3endo,2}$ = $^3J_{3endo,4}$ = 11.7, H3*endo*), 1.91 (m, H6*endo*, H7*endo*), 1.83 (d of t, $^2J_{8anti,8syn}$ = 12.7 Hz, $^3J_{8anti,1}$ = $^3J_{8anti,5}$ = 5.3 Hz, H8*anti*), 1.73 (m, H6*exo*, H7*exo*), 1.55 (d, $^2J_{8syn,8anti}$ = 12.7 Hz, H8*syn*). ^{13}C NMR δ_C ($CDCl_3$): 53.2 (C2, C4), 42.7 (C1, C5), 41.3 (C3), 38.7 (C8), 24.4 (C6, C7). HRMS: $C_8H_{12}{}^{81}Br_2$ M$^{\bullet+}$ requires 269.9267, found 269.9278 (2.1); $C_8H_{12}{}^{79}Br{}^{81}Br$ M$^{\bullet+}$ requires 267.9287, found 267.9457 (4.7); $C_8H_{12}{}^{79}Br_2$ M$^{\bullet+}$ requires 265.9307, found 265.9384 (3.4). **2-*endo*,6-*endo*-Dibromobicyclo[3.2.1]octane** (**12**) was obtained as a white solid. ^{1}H NMR δ_H ($CDCl_3$): 4.38 (m, $^3J_{6,5}$ = $^3J_{6,7endo}$ = 5.6 Hz, $^3J_{6,7exo}$ = 10.7 Hz, H6), 4.25 (m, $^4J_{2,7exo}$ = 1.0 Hz, H2), 2.56 (m, H1), 2.49 (m, $^3J_{7exo,6}$ = 11.0 Hz, $^4J_{7exo,2}$ =

(52) Ouellette, R. J.; Robins, R. D.; South, A., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 1619.
(53) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256.

1.2 Hz, H7*exo*), 2.33 (m, H5), 2.12* (H7*endo*), 2.14–2.22 (m, H3*endo*, H3*exo*), 1.99 (m, $^2J_{4endo,4exo}$ = 16.2 Hz, $^4J_{4endo,8anti}$ = 2.9 Hz, H4*endo*), 1.77 (m, H8*anti*), 1.65* ($^4J_{8syn,7endo}$ = 3.0 Hz, H8*syn*), 1.57* (H4*exo*). ^{13}C NMR δ_C ($CDCl_3$): 56.5 (C2), 51.1 (C6), 44.8 (C1), 38.8 (C5), 38.0 (C8), 36.4 (C7), 30.9 (C3), 30.4 (C4). LRMS: $C_8H_{12}{}^{81}Br_2$ $M^{\bullet+}$ requires 270, found 270 (0.2); $C_8H_{12}{}^{79}Br{}^{81}Br$ $M^{\bullet+}$ requires 268, found 268 (0.3); $C_8H_{12}{}^{79}Br_2$ $M^{\bullet+}$ requires 266, found 266 (0.2); $C_8H_{12}{}^{81}Br$ $[M - Br]^+$ requires 189, found 189 (85); $C_8H_{12}{}^{79}Br$ $[M - Br]^+$ requires 187, found 187 (86). HRMS: $C_8H_{12}{}^{81}Br$ $[M - Br]^+$ requires 189.0103, found 189.0102 (100.0).

Attempted Synthesis of Bicyclo[3.2.1]oct-2-ene (18) by Reaction of *endo*-Tricyclo[3.2.1.0^{2,4}]octane (11) with acid in Carbon Tetrachloride. Trifluoroacetic acid (1 drop) was added to a solution of **11** (16 mg, 0.15 mmol) in CCl_4 (1 mL), the solution was stirred at room temperature and the progress of the reaction was monitored by ^{1}H NMR. After 6 days a ^{1}H NMR spectrum showed no significant reaction. The reaction was then heated to 70 °C for a further 6 days after which time a ^{1}H NMR spectrum of the resulting mixture again showed that no reaction had occurred. A catalytic amount of HBr in acetic acid was added and the reaction continued at room temperature for 12 days. A ^{1}H NMR spectrum after this time showed no reaction. The solution was heated to 70 °C for a further 14 days, but again no significant reaction was observed by ^{1}H NMR after this time.

Reaction of *endo*-Tricyclo[3.2.1.0^{2,4}]octane (11) with Bromine in Methanol. To a stirred solution of **11** (117 mg, 1.08 mmol) in dry methanol (3 mL) was added bromine (154 mg, 0.96 mmol, 0.89 mol equiv) in dry methanol (5 mL) dropwise over 10 min. The solution was stirred at room temperature for 2 h after which time the reaction was diluted with water (8 mL) and sodium metabisulfite added until all of the bromine color had dissipated. The solution was extracted with ether (20 mL), the ether extracts were washed with water and dried over $MgSO_4$, and the solvent was removed under reduced pressure to give a yellow oil (132 mg, ca. 60% recovery). GLC analysis showed the presence of three products, 2-*endo*-bromo-4-*endo*-methoxybicyclo[3.2.1]octane (**19**) (53%), 6-*endo*-bromo-2-*endo*-methoxybicyclo[3.2.1]octane (**20**) (44%), and 2-*endo*-4-*endo*-dibromobicyclo[3.2.1]octane (**13**) (3%). A crude separation was effected by radial chromatography (2 mm PEG coated silica plate, pentane elution). The major products were further purified by preparative TLC (analytical grade silica TLC plates, 1% ethyl acetate/pentane elution). 2-*endo*,4-*endo*-Dibromobicyclo[3.2.1]octane (**13**) was identified by comparison of its ^{1}H NMR data with that reported above. **2-*endo*-Bromo-4-*endo*-methoxybicyclo[3.2.1]octane (19)** was obtained as a colourless oil. ^{1}H NMR δ_H ($CDCl_3$): 4.12 (m, $^3J_{2,1}$ = 2.0 Hz, $^3J_{2,3endo}$ = 11.3 Hz, $^3J_{2,3exo}$ = 5.4 Hz, H2), 3.29 (s, $W_{h/2}$ = 1.0 Hz, OMe), 3.17 (m, $^3J_{4,3endo}$ = 12.2 Hz, $^3J_{4,3exo}$ = 5.2 Hz, $^3J_{4,5}$ = 2.3 Hz, H4), 2.46* (H1), 2.44# (m, H3*exo*), 2.41* (H5), 1.80* (H7*endo*), 1.75* (H6*endo*), 1.71# (d of t, $^2J_{8anti,8syn}$ = 11.7 Hz, $^3J_{8anti,1}$ = $^3J_{8anti,5}$ = 5.9 Hz, H8*anti*), 1.69# (d of t, $^2J_{3endo,3exo}$ = 13.0 Hz, $^3J_{3endo,2}$ = $^3J_{3endo,4}$ = 10.9 Hz, H3*endo*), 1.62* (H7*exo*), 1.56* (H6*exo*), 1.33 (d, $^2J_{8syn,8anti}$ = 12.2 Hz, H8*syn*). ^{13}C NMR δ_C ($CDCl_3$): 80.5 (C4), 55.8 (OMe), 53.8 (C2), 43.4 (C1), 37.1 (C5), 37.0 (C3), 35.6 (C8), 24.7 (C7), 22.8 (C6). HRMS: $C_9H_{15}{}^{79}BrO$ $M^{\bullet+}$ requires 218.0307, found 218.0375 (46.0); $C_9H_{15}O$ $[M - Br]^+$ requires 139.1123, found 139.1133 (55.6). **6-*endo*-Bromo-2-*endo*-methoxybicyclo[3.2.1]octane (20)** was obtained as a colorless oil. ^{1}H NMR δ_H ($CDCl_3$): 4.36 (m, $^3J_{6,7endo}$ = 5.7 Hz, $^3J_{6,7exo}$ = 10.7 Hz, H6), 3.30 (s, $W_{h/2}$ = 0.6 Hz, OMe), 3.24 (m, $^3J_{2,1}$ = $^3J_{2,3exo}$ = 3.4 Hz, $^3J_{2,3endo}$ = 10.3 Hz, H2), 2.37 (m, H1), 2.29 (m, H7*exo*), 2.20 (m, H5), 1.99 (m, $^2J_{7endo,7exo}$ = 14.5 Hz, $^3J_{7endo,6}$ = 5.6 Hz, $^4J_{7endo,8syn}$ = 2.5 Hz, H7*endo*), 1.97* (H4*endo*), 1.89* (H3*exo*), 1.70 (m, $^2J_{8anti,8syn}$ = 12.3 Hz, $^3J_{8anti,1}$ = $^3J_{8anti,5}$ = 5.4 Hz, $^4J_{8anti,4endo}$ = 2.9 Hz, H8*anti*), 1.51* (H3*endo*), 1.47* (H4*exo*), 1.44 (d of d, $^2J_{8syn,8anti}$ = 12.0 Hz, $^4J_{8syn,7endo}$ = 2.7 Hz, H8*syn*). ^{13}C NMR δ_C ($CDCl_3$): 80.8 (C2), 55.4 (OMe), 52.5 (C6), 39.4 (C5), 38.6 (C1), 35.2 (C8), 35.0 (C7), 27.7 (C4), 25.2 (C3). LRMS: $C_9H_{15}{}^{81}BrO$ $M^{\bullet+}$ requires 220, found 220 (0.7); $C_9H_{15}{}^{79}BrO$ $M^{\bullet+}$ requires 218, found 218 (0.7). HRMS: $C_9H_{15}{}^{79}BrO$ $M^{\bullet+}$ requires 218.0307, found 218.0327 (30.9).

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Supplementary Material Available: Copies of ^{1}H and ^{13}C NMR spectra of all new compounds (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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