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Intramolecular Bromonium Ion Assisted Epoxide Ring-Opening: Capture of the Oxonium Ion with an Added External Nucleophile

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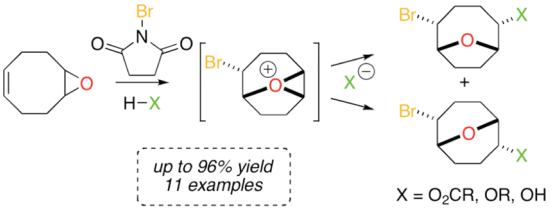

9-Oxabicyclo[6.1.0]non-4-ene (**1**) undergoes intramolecular bromonium ion-assisted epoxide ring-opening using *N*-bromosuccinimide via a presumed oxonium ion that is subject to stereospecific, nonregioselective capture with added external nucleophiles producing novel bicyclo[4.2.1] and bicyclo-[3.3.1] ethers. Carboxylic acids (as catalyzed by tetramethylguanidine), alcohols, water, and halides can all function as effective nucleophiles. Stereospecific direct opening of the bromonium ion with carboxylic acids was found to be a competing process where high dilution disfavors this pathway. Halogen-induced isotopic ^{13}C NMR shifts ($\Delta\delta$ *C*Br 1.3−1.9 ppb; $\Delta\delta$ *C*Cl 8.6−8.7 ppb) were found to be most useful in unambiguously identifying halogen-bearing carbons, and correlation of these ^{13}C NMR shifts allowed ready assignment of diastereomeric structures. The structure of adducts **6b**, **6c**, **7b**, **7c**, **7d**, and **8a**−**d** were all elucidated by X-ray crystallography.

Introduction

The formation of a bromonium ion[1−8] by the action of electrophilic bromine on an alkene followed by stereospecific trapping by a nucleophile to give a 1,2-addition product is a fundamental reaction in organic chemistry.[9] In 1985, a further reactivity mode was reported whereby in the reaction of an epoxyalkene with molecular bromine, intramolecular trapping of the bromonium ion by the epoxide oxygen occurred, and a presumed resultant oxonium ion was captured by the necessarily present bromide anion (Scheme 1, case a).[10a] Although mixtures of ethereal dibromide products were produced by nonregioselective ring-openings, only those diastereomers of stereospecific backside opening of the bromonium ion by the epoxide oxygen and subsequent stereospecific backside attack on the resultant oxonium ion were formed. The same authors later reported that the intermolecular reaction of alkenes and epoxides with molecular bromine could proceed along the same pathway with the same stereochemical outcome (Scheme 1, case a).[10b]

More recently, both McDonald[11] and Jamison[12] have demonstrated the use of electrophilic bromine sources (bromonium

(1) For a review see: Ruasse, M.-F. *Acc. Chem. Res.* **1990**, *23*, 87–93. and references cited therein.
(2) The 3-membered cyclic bromonium ion was first suggested by Roberts and Kimball: Roberts, I.; Kimball, G. E. *J. Am. Chem. Soc.* **1937**, *59*, 947–948.
(3) For evidence that the bromonium ion is cyclic and symmetrical see: Winstein, S.; Lucas, H. J. *J. Am. Chem. Soc.* **1939**, *61*, 2845–2848.
(4) For the observation of bromonium ions by NMR see: (a) Olah, G. A.; Bollinger, J. M.; Brinich, J. *J. Am. Chem. Soc.* **1968**, *90*, 2587–2594. (b) Olah, G. A.; Bollinger, J. M. *J. Am. Chem. Soc.* **1968**, *90*, 6082–6086.
(5) For the first isolable bromonium ion see: Strating, J.; Wieringa, J. H.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* **1969**, 907–908.
(6) For X-ray characterisation of stable bromonium ions see: (a) Slebocka-Tilk, H.; Ball, R. G.; Brown, R. S. *J. Am. Chem. Soc.* **1985**, *107*, 4504–4508. (b) Bennet, A. J.; Brown, R. S.; McClung, R. E. D.; Klobukowski, M.; Aarts, G. H. M.; Santarsiero, B. D.; Bellucci, G.; Bianchini, R. *J. Am. Chem. Soc.* **1991**, *113*, 8532–8535. (c) Brown, R. S.; Nagorski, R. W.; Bennet, A. J.; McClung, R. E. D.; Aarts, G. H. M.; Klobukowski, M.; McDonald, R.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1994**, *116*, 2448–2456. (d) Brown, R. S. *Acc. Chem. Res.* **1997**, *30*, 131–137.
(7) For the first generation and trapping of enantiomerically pure bromonium ions see: Braddock, D. C.; Hermitage, S. A.; Kwok, L.; Pouwer, R.; Redmond, J. M.; White, A. J. P. *Chem. Commun.* **2009**, 1082–1084.
(8) On the absolute configurational stability of bromonium ions in the presence of alkenes see: Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232–1233.
(9) Olah, G. A.; Laali, K. K.; Wang, Q.; Prakash, G. K. S. *Onium Ions*; John Wiley & Sons: New York, 1998.
(10) (a) Davies, S. G.; Polywka, M. E. C.; Thomas, S. E. *Tetrahedron Lett.* **1985**, *26*, 1461–1464. (b) Davies, S. G.; Polywka, M. E. C.; Thomas, S. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1277–1282.

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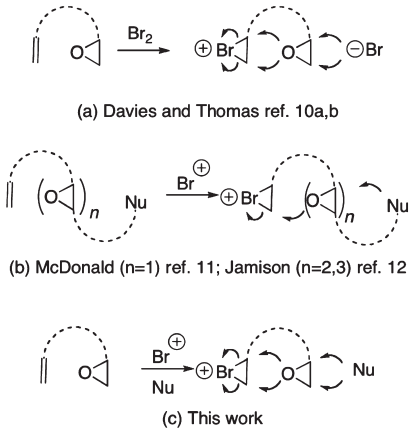
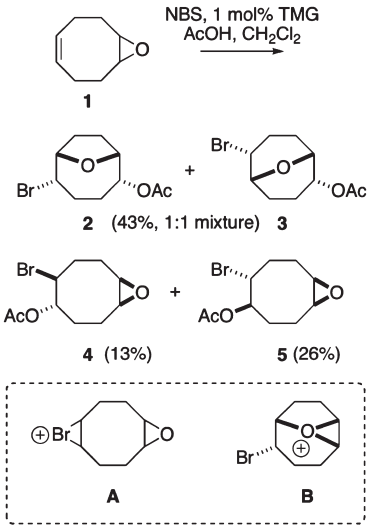
SCHEME 1. Generalized Modes of Intramolecular Bromonium Ion-Assisted Epoxide Ring-Openings



di-*sym*-collidine perchlorate and NBS, respectively) to effect spectacular intramolecular bromonium ion assisted epoxide ring-openings, to construct complex (poly)cyclic ether compounds, where the final cyclization is terminated by an intramolecularly positioned nucleophile (Scheme 1, case b). In these systems, the regioselectivity of ring-closure was effectively controlled by the substitution pattern of the substrate, and stereospecific ring-openings occurred, although the bromonium ion formation was not face selective. The latter work allowed for the total synthesis of *ent*-dioxepandehydrothyrsiferol and demonstrated the feasibility of this route as a biogenetic pathway in *Laurencia* species. To date, however, there have been no reports on intramolecular bromonium ion-assisted epoxide ring-opening with an added external nucleophile (Scheme 1, case c).[13] Such a method should provide additional flexibility in building (poly)cyclic ether compounds with different functional groups. However, in such systems there is an additional inherent selectivity question—whether the added external nucleophile will attack directly the bromonium ion of the original olefin or whether the formation of an oxonium ion followed by its trapping will predominate. Herein we report the first examples of intramolecular bromonium ion assisted epoxide ring-expansions with trapping of the presumed resultant oxonium ion[14] by added external nucleophiles. In particular, we report that the use of water[15] as the solvent (and nucleophile) gives rise to exclusive trapping of the oxonium ion in preference to the original bromonium ion.

SCHEME 2. Bromoether Formation by Capture with an Added Nucleophile



Results and Discussion

We selected 9-oxabicyclo[6.1.0]non-4-ene (**1**)[10a] as a suitable alkene epoxide substrate and *N*-bromosuccinimide (NBS) as the source of electrophilic bromine. A carboxylic acid was selected as a suitable nucleophile which can provide a proton to produce succinimide as the neutral byproduct. However, initial experiments with alkene epoxide **1** and NBS, with acetic acid as the added nucleophile, in dichloromethane, failed to give any reaction. To our delight, the addition of catalytic quantities (1 mol %) of tetramethylguanidine (TMG)[16] led to rapid reaction giving the previously unreported [4.2.1]bicycloether **2** and [3.3.1]bicycloether **3** (as an inseparable 1:1 mixture, 43%) and novel bromoacetates **4** (13%) and **5** (26%) after purification by column chromatography (Scheme 2). The identities and stereochemistries of these diastereomeric compounds with identical molecular formulas were unambiguously proven by a combination of X-ray crystallography, NMR methods, and correlation by interconversion (*vide infra*). In the reaction itself, a bromonium ion **A** can evidently be trapped intramolecularly by the epoxide to give an oxonium ion **B**. This can only occur when the bromonium ion and epoxide are on opposite faces (where presumably the bromonium ion can be formed reversibly on either face of the alkene). The oxonium ion **B** can in turn be trapped with an added external nucleophile (acetate) giving **2** and **3**. A control experiment without NBS showed that the epoxide is not ring-opened by acetic acid under these conditions. A further possible isomer could possibly be envisioned by opening of the oxonium ion **B** α-to the carbon bearing bromine. This would lead to a *syn*-bromocarboxylate (not shown) by double inversion at this center. Such a compound was not detected in this or any other series. This implies that the bromine is an effective steric shield for ring-opening of the oxonium ion at this position. Alternatively, the bromonium ion **A** can be directly trapped by acetate giving bromoacetates **4** and **5** with the epoxide left intact. In this

(11) Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *Org. Lett*. **2004**, *6*, 4487–4489.

(12) Tanuwidjaja, J.; Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc*. **2009**, *131*, 12084–12085.

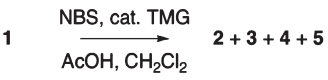
(13) (a) For the intramolecular capture of a bromonium ion with the oxygen of a THF and opening of the oxonium ion with an external nucleophile see: Braddock, D. C.; Millan, S.; Perez-Fuertes, Y.; Pouwer, R. H.; Sheppard, R. N.; Solanki, S.; White, A. J. P. *J. Org. Chem*. **2009**, *74*, 1835–1841 and references cited therein. An electrophilic aminoalkoxylation of olefins featuring the intermolecular capture of a bromonium ion by an epoxide followed by capture of the oxonium intermolecularly by an amine has been reported: (b) Zhou, L.; Tan, C. K.; Zhou, J.; Yeung, Y.-Y. *J. Am. Chem. Soc*. **2010**, *132*, 10245–10247.

(14) For a report of an extraordinarily stable oxonium ion see: Mascal, M.; Hafezi, N.; Meher, N. K.; Fettinger, J. C. *J. Am. Chem. Soc*. **2008**, *130*, 13532–13533.

(15) For the use of water as solvent for promoting endoselective epoxide-opening cascades see: (a) Morten, C. J.; Jamison, T. F. *J. Am. Chem. Soc*. **2009**, *131*, 6678–6679. (b) Byers, J. A.; Jamison, T. F. *J. Am. Chem. Soc*. **2009**, *131*, 6383–6385. (c) Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189–1192.

(16) For the use of TMG as a catalyst for bromolactonisation and intermolecular bromoacetoxylation see: Ahmad, S. M.; Braddock, D. C.; Cansell, G.; Hermitage, S. A. *Tetrahedron Lett*. **2007**, *48*, 915–918.

TABLE 1. Concentration Dependent Product Distribution



entry[a]	[**1**] mol dm^{-3}	% conversion[b]	**2** + **3**: **4** + **5**[b]
1	0.25	99	30:70
2	0.025	95	55:45
3	0.0025	63	80:20
4	0.00025	72[c]	85:15

[a]All reactions performed with 1.0 equivalent of NBS, 15 μL of TMG and 1.0 equivalent of AcOH for 2.5 h at rt (see Supporting Information). [b]As determined by inspection of the ^{1}H NMR spectrum of the crude reaction mixture (see Supporting Information). [c]After a reaction time of 72 h.

eventuality, the external nucleophile can trap the bromonium ion regardless of which face it has been formed giving rise to two bromoacetate epoxide diastereoisomers. The relative stereochemistries of the products show that both bromonium and oxonium ion trapping are stereospecific (albeit not regioselective) giving a total of only four possible products.

In an effort to further favor the formation of bromoethers **2** and **3** over bromoacetates **4** and **5**, we explored the effect of concentration on the reaction. Inspection of the results (Table 1) show a marked concentration dependence on the relative ratios of bicyclo ethers **2** and **3** versus bromoacetates **4** and **5**, with the former being favored at high dilution.[17]

A series of other carboxylic acids as added external nucleophiles were then utilized (Table 2). Thus benzoic acid, *p*-nitrobenzoic acid and 2,3,4,5-tetrafluorobenzoic acid as added nucleophiles under the optimized conditions shown gave bicycloethers **6a**−**c** and **7a**−**c** along with the bromoacetates **8a**−**c** and **9a**−**c** (entries 1−5) respectively. A concentration effect is again in operation (entry 1 vs entry 2 and entry 4 vs entry 5) and the use of more dilute solutions (entries 2 and 5) provided the bicycloethers as the major products of these reactions in high yields. The relative ratio of all the bicycloethers was approximately unity in these cases, indicating indiscriminate attack at either position of oxonium ion **B** by the nucleophile. The benzoate ethers **6a** and **7a** were formed as an inseparable mixture, while the *p*-nitrobenzoate ethers **6b** and **7b**, and the tetrafluorobenzoate ethers **6c** and **7c** could be separated by column chromatography and by HPLC respectively. Chloride could be incorporated to give **6d** and **7d** in excellent yield by the use of TMSCl and catalytic TMG in CH_2Cl_2 (entry 6). Alternatively the use of LiCl in wet CH_3CN gave the same bicyclic ethers along with small quantities of bromochloride epoxides **8d** and **9d** (entry 7). In both cases the yield of the bicyclic ethers **6d** and **7d** is good even in relatively concentrated solution, but there is no marked preference for one ring system over the other. Alcohols (MeOH, EtOH) could be utilized as nucleophiles by the action of NBS in the alcohol as solvent (entries 8,9) (the use of added methanol in dichloromethane gave only poor conversions and gave rise to dibromide side-products) to give bicycloethers **6e** and **7e**, and **6f** and **7f** respectively, both as inseparable mixtures. Trace quantities of epoxides from direct opening of the bromonium ion by methanol were apparent, but in insufficient quantities to be isolated and fully characterized. In these cases there is a slight preference (2−3:1) for the [3.3.1]bicycloether as the major diastereoisomer. The use of water as solvent produced ether products **6g** and **7g**[18] exclusively in excellent yields, regardless of the concentration (entries 10,11,12), again with a slight preference (ca. 3:1) for the [3.3.1]bicycloether as the major diastereoisomer. Finally, we prepared the known dibromides **6h** and **7h** as an inseparable mixture by the action of molecular bromine on epoxyalkene **1** in carbon tetrachloride (entry 13).[10a] These experiments show that the intramolecular bromonium ion assisted epoxide ring-opening is a favorable and high-yielding process that can occur with a variety of added external nucleophiles (carboxylic acids, alcohols, water and halides). In polar solvents (which also function as the nucleophile) this process is highly favored over direct attack of the nucleophile on the bromonium ion. Under these conditions the [3.3.1]bicycloether is the slightly preferred diastereoisomer. In chlorinated solvents the intramolecular bromonium ion assisted epoxide ring-opening with carboxylic acids as added nucleophiles can be rendered favorable in dilute solution.

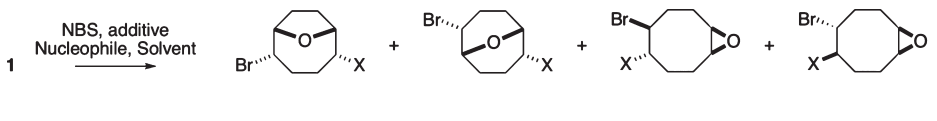
Both bicycloethers in the *p*-nitro- (**6b**, **7b**) and tetrafluoro- (**6c**, **7c**) benzoate series were crystalline and their structures were solved by X-ray crystallography (Figure 1, **6b** and **7b**. For **6c** and **7c** see the Supporting Information). Chloride **7d** could be obtained by HPLC separation, and was also crystalline, and was also confirmed as the [3.3.1]bicycloether by X-ray crystallography (see the Supporting Information).[19] These structures confirm the expected *anti* relationship between both the bromide and ether oxygen and the *anti* relationship between the ether oxygen and the benzoate group, showing that bromonium ion opening by the epoxide, and subsequent oxonium ion opening are completely stereospecific. The tetrafluorobenzoate ethers **6c** and **7c** were hydrolyzed under basic conditions to the alcohols **6g** and **7g** respectively (thus confirming the latter's structures). Individual samples of authentic acetates **2** and **3**, benzoates **6a** and **7a** and methyl ethers **6e** and **7e** (thus confirming their structures), were then prepared by standard methods from the free alcohols **6g** and **7g** by acetylation, benzoylation and methylation respectively (see Supporting Information). With the stereochemistry all secured for all the novel bicyclic ethers bar **6d**, **6f**, and **7f**, inspection of all the ^{13}C NMR spectra reveals a strong correlation for the [4.2.1] ethers where the carbon bearing the bromine

(17) This effect is not easy to rationalize. Assuming that the attack of acetate is the rate-determining step (and irreversible) then the product distribution should remain unchanged with changing concentration. Oxonium ion **B** or bromonium ion **A** could not be observed by ^{1}H NMR monitoring of the reaction mixtures indicating that neither intermediate accumulates. The position of the expected rapid equilibrium between **A** and **B** is expected also to be concentration independent. One referee helpfully suggested that "If one makes the alternative assumption that bromonium ion **A** and oxonium ion **B** are *not* in rapid equilibrium, then the product distribution is the result of the relative rates of formation of **B** versus external nucleophilic attack on **A**. Higher dilution then favors the intramolecular attack to form **B**, which may then react with the added nucleophile at its leisure."

(18) These alcohols have been reported previously as a 7:1 inseparable mixture, by bromination of an epoxydiol: Takahashi, A.; Aso, M.; Tanaka, M.; Suemune, H. *Tetrahedron* **2000**, *56*, 1999–2006.

(19) The X-ray data is unable to distinguish between the mixed halogen species and a mixture of the dibromo and dichloro species for **7d** (see Supporting Information for a full discussion). However, there is no doubt that this is the mixed bicyclo[3.3.1]bromochloride: the ^{13}C NMR spectrum has 8 different ^{13}C NMR resonances with the resonance at 50.3 ppm showing a distinctive bromine isotope effect ($\Delta\delta$ [$C^{79}Br$,$C^{81}Br$] = 1.8 ppb) and the resonance at 57.6 ppm showing a distinctive chlorine isotope effect ($\Delta\delta$ [$C^{35}Cl$,$C^{37}Cl$] = 8.7 ppb). See also ref 20. The mass spectrum also shows the distinctive isotope pattern for a monochloromonobromide [m/z=242 (24%), 240 (100%), 238 (76%): $M^{+\cdot}$].

TABLE 2. Bromonium Ion-Assisted Epoxide Ring-Opening of 1 with Added External Nucleophile



6a; X = OBz
6b; X = OBz-4-NO_2
6c; X = OBz-2,3,4,5-F_4
6d; X = Cl
6e; X = OMe
6f; X = OEt
6g; X = OH
6h; X = Br

7a; X = OBz
7b; X = OBz-4-NO_2
7c; X = OBz-2,3,4,5-F_4
7d; X = Cl
7e; X = OMe
7f; X =OEt
7g; X = OH
7h; X = Br

8a; X = OBz
8b; X = OBz-4-NO_2
8c; X = OBz-2,3,4,5-F_4
8d; X = Cl

9a; X = OBz
9b; X = OBz-4-NO_2
9c; X = OBz-2,3,4,5-F_4
9d; X = Cl

entry	nucleophile (equiv)	solvent	additive	*T* (h)	[C]	**6**[a]	**7**[a]	**8**	**9**	total yield
1[b]	$PhCO_2H$ (1.1)	CH_2Cl_2	1 mol % TMG	6	0.22 M	**6a** and **7a**[c] (50%) 0.9: 1[d]		**8a** (22%)	**9a** (8%)	80%
2[b]	$PhCO_2H$ (1.1)	CH_2Cl_2	1 mol % TMG	6	0.0025 M	**6a** and **7a**[c] (81%) 1: 0.9 [d]		**8a** (2%)	**9a** (2%)	85%
3[b]	4-NO_2PhCO_2H (1.1)	CH_2Cl_2	1 mol % TMG	3	0.0026 M	**6b** (41%)	**7b** (42%)	**8b** (11%)	**9b** (4%)	98%
4[b]	2,3,4,5-F_4−$PhCO_2H$ (1.1)	CH_2Cl_2	1 mol % TMG	6	0.25 M	**6c** and **7c**[c] (33%) 0.6: 1[d]		**8c** (4%)	**9c** (2%)	39%
5[b]	2,3,4,5-F_4−$PhCO_2H$ (1.1)	CH_2Cl_2	1 mol % TMG	3	0.0042 M	**6c** (22%)[e]	**7c** (22%)[e]	**8c** (10%)	**9c** (4%)	58%
6[f]	TMSCl (1.1)	CH_2Cl_2	1 mol % TMG	4	0.08 M	**6d** and **7d**[c] (90%) 1.4: 1[d]		**8d** (0%)	**9d** (0%)	90%
7[f]	LiCl (15)	MeCN	−	1	0.22 M	**6d** and **7d**[c] (86%) 1.2: 1[d]		**8d** and **9d**[b] (8%) 9: 1		94%
8[f]	MeOH	MeOH	−	6.5[g]	0.25 M	**6e** and **7e**[c] (52%) 1: 2.1[d,h]		−	−	58%
9[f]	EtOH	EtOH	−	9.5	0.25 M	**6f** and **7f**[c] (51%) 1: 3.2[d]		−	−	51%
10[f]	H_2O	H_2O	−	2.5	0.25 M	**6g** and **7g**[d] (84%) 1: 3.2[d]		−	−	84%
11[f]	H_2O	H_2O	−	2.5	0.025 M	**6g** and **7g**[c] (96%) 1: 3.0[d]		−	−	96%
12[f]	H_2O	H_2O	−	2.5	0.0025 M	**6g** and **7g**[c] (86%) 1: 3.2[d]		−	−	86%
13[f]	Br_2	CCl_4	−	3	0.2 M	**6h** and **7h**[c] (48%) 1: 1[d]		−	−	48%

[a]Compounds **6a**−**h** and **7a**−**h** were found to be indefinitely stable at room temperature in chlorinated solvents. Thus under the conditions of the reaction no isomerization between the two is occurring, and the product ratios reflect the kinetic product distribution and not an equilibrium position. [b]Two equivalents of NBS. [c]Products were inseparable by flash column chromatography. [d]Ratio determined by ^{1}H NMR spectroscopy. [e]Isolated yield after HPLC separation. [f]NBS (1.0−1.3 equiv). [g]The use of catalytic quantities of TMG resulted in the reaction going to completion in 4 h, but the isolated yield of **6e** and **7e** was reduced at 43% (1: 2.8). [h]Average of two runs after chromatography.

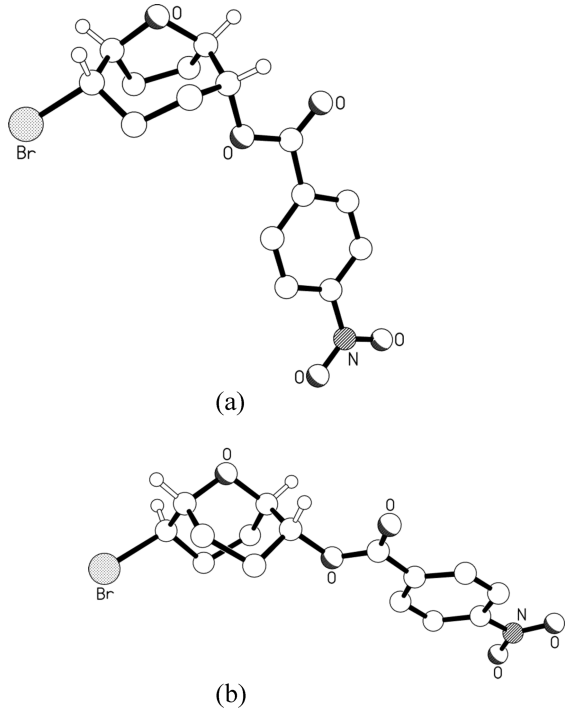


FIGURE 1. (a) Molecular structure of **6b**. (b) Molecular structure of **7b**.

atom resonates invariantly in the region 54 ± 1 ppm. The same resonance is seen at 50.5 ± 1 ppm for the [3.3.1]bicyclic compounds. For a given substituent, the difference between these chemical shifts is $\Delta\delta \geq 3$ ppm, thus providing a quick and convenient method for identification of the different ring systems (Table 3). Chloride **6d** and ethyl ethers **6f** and **7f** were then assigned on the basis of their bromine-bearing carbon resonances at 53.4, 54.7, and 51.4 ppm respectively. The known dibromides[10a] **6h** (53.4 ppm) and **7h** (50.4 ppm) were also found to conform to this model. Moreover, bromide-induced isotopic NMR shifts were most useful in unambiguously identifying these carbons as the bromide bearing ones (Figure 2, see also Supporting Information).[20]

The bromoepoxides **8a**, **8b**, **8c** and **8d**[21] were also unambiguously identified by X-ray crystallography (Figure 3a−d). Evidently, bromonium ions have been trapped directly by the nucleophile to give an *anti* arrangement of functional groups by stereospecific ring-opening. The diastereomeric epoxide products **9a**−**9d** must come from ring-opening of the bromonium ion when formed on the other face of the olefin. Interestingly, bromotetrafluorobenzoate epoxide **9c** proved to be unstable on standing, and produced **6c**, **7c**, **8c** (and **9c**) in ratios comparable to those observed in the reaction detailed in Table 2, entry 5. This can be rationalized by invoking bromonium ion formation in **9c** by neighboring group participation of the

(20) (a) For bromine-induced isotopic shifts see: Raynes, W. T.; Sergeyev, N. M.; Sandor, P.; Grayson, M. *Magn. Reson. Chem.* **1997**, *35*, 141–143. (b) For chlorine-induced isotopic shifts see: Sergeyev, N. M.; Sergeyeva, N. D.; Raynes, W. T. *J. Magn. Reson, Ser. A* **1995**, *115*, 174–182. (c) For the use of these methods to distinguish bromochloride regioisomers after opening of a bromonium ion with chloride see ref 7. (d) For the use of these methods in natural product structure elucidation see ref 13 and references cited therein.

(21) Modeling of the disorder in the X-ray crystal structure of **8d** means that for 88% of the molecules in the crystal the bromide is on the same side of the ring as the epoxide oxygen, whilst in the remaining 12% it is the chloride that is the same side as the oxygen (i.e., the minor diastereoisomer **9d**). This is consistent with the ratio of the diastereoisomers (9:1) observed as an inseparable mixture by ^{1}H NMR and implies cocrystallisation.

TABLE 3. Correlation of ^{13}C NMR Chemical Shifts for the Carbon-Bearing Bromine for 2, 3, 6a−h, and 7a−h[a]

X	δ *C*Br (ppm)	δ *C*Br (ppm)	Δδ (ppm)
OAc	**2**; 53.70	**3**; 50.56	+3.14
OBz	**6a**; 53.64	**7a**; 50.58	+3.06
OBz-4-NO_2	**6b**; 53.23	**7b**; 50.14	+3.09
OBz-2,3,4,5-F_4	**6c**; 53.17	**7c**; 50.18	+2.99
Cl	**6d**; 53.38	**7d**; 50.34	+3.04
OMe	**6e**; 54.56	**7e**; 51.17	+3.39
OEt	**6f**; 54.73	**7f**; 51.37	+3.36
OH	**6g**; 54.30	**7g**; 51.04	+3.26
Br	**6h**; 53.41	**7h**; 50.35	+3.06

[a]All spectra were recorded in $CDCl_3$.

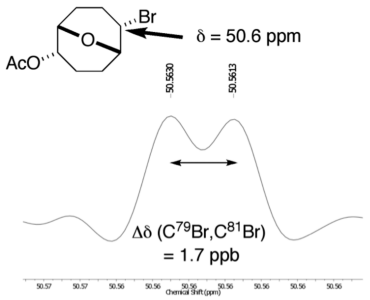


FIGURE 2. Bromide-induced isotopic shift for the *C*Br resonance of **3** at 50.6 ppm (125 MHz, $CDCl_3$).

bromine and loss of tetrafluorobenzoate. The resultant bromonium ion **A** (c.f. Scheme 2) can now be trapped by the epoxide and the oxonium ion **B** trapped by the earlier expelled tetrafluorobenzoate anion. The formation of **8c** also implies concomitant reversible loss of electrophilic bromine from the bromonium ion to the bulk medium[8] and return to the other face of the alkene and recapture by tetrafluorobenzoate. To the best of our knowledge the spontaneous formation of a bromonium ion by NGP of bromide on a suitably positioned leaving group is unprecedented, and this observation may be useful in designing further systems for the generation of enantiopure bromonium ions starting from enantiopure bromohydrins.[7] It also implicitly confirms the expected *anti* relationship between the bromine and tetrafluorobenzoate group in **9c**. Bromoacetate epoxides **4** and **5** were assigned by comparison of the ^{13}C NMR spectral data for the bromine-bearing carbons (Table 4) with those of esters **8a−c** and **9a−c** respectively. Here again, the bromide-induced isotopic NMR shifts were most useful in unambiguously identifying these carbons as the bromide bearing ones (see Supporting Information).[20]

Bromotetrafluorobenzoate epoxide **9c** was saponified to give the known *syn*-diepoxide **10** (Scheme 3).[22,23] This

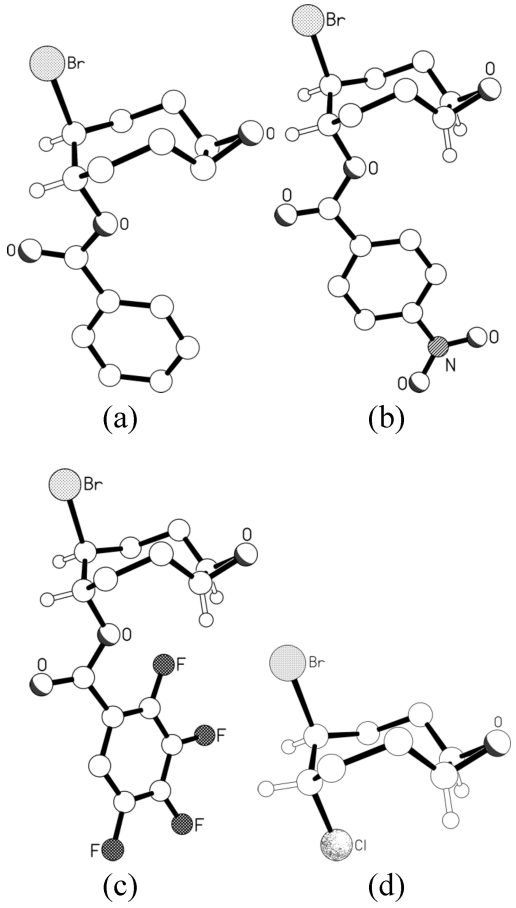


FIGURE 3. (a) Molecular structure of one (**8a-I**) of the two crystallographically independent C_S-symmetric molecules present in the crystals of **8a** (see Supporting Information). (b) Molecular structure of **8b**. (c) Molecular structure of **8c**. (d) Molecular structure of the C_S-symmetric species **8d** (see Supporting Information).

TABLE 4. Correlation of ^{13}C NMR Chemical Shifts for the Carbon-Bearing Bromine for 4, 5, 8a−c, and 9a−c[a]

X	δ *C*Br (ppm)	δ *C*Br (ppm)	Δδ (ppm)
OAc	**4**; 50.99	**5**; 53.67	+2.68
OBz	**8a**; 50.59	**9a**; 52.46	+1.87
OBz-4-NO_2	**8b**; 50.51	**9b**; 53.51	+3.00
OBz-2,3,4,5-F_4	**8c**; 50.27	**9c**; 52.52	+2.25

[a]All spectra were recorded in $CDCl_3$.

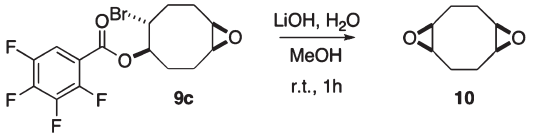
unambiguously confirms the assigned stereochemistry for **9c**, and by analogy the stereochemistries of **5** and **9a−b**.

Finally, we recognized that a peracid epoxidation of inexpensive 1,5-cyclooctadiene (**11**) would deliver epoxyalkene **1** and produce a stoichiometric quantity of carboxylic acid as side-product. This carboxylic acid could subsequently also function as an *in situ* external added nucleophile in the presence of a suitable electrophilic bromine source, to provide bicyclo[4.2.1] and bicyclo[3.3.1]ethers, thereby constructing products with four stereocenters with complete control of relative stereochemistry in one-pot and with good atom

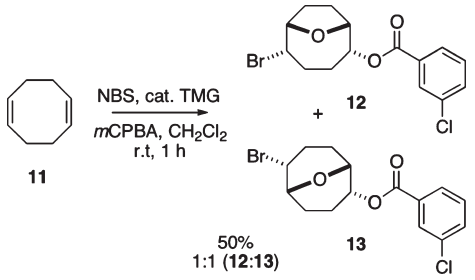
(22) Rudolph, J.; Reddy, K. L.; Chiang, J. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 6189–6190.

(23) Saponification of bromobenzoate **8c** under the same conditions led to the formation of the expected diastereomeric epoxide and competitive formation of alcohols **6g** and **7g.** The pre-existing epoxide evidently suffers intramolecular nucleophilic attack by the alkoxide generated from collapse of the tetrahedral intermediate during $B_{Ac}2$ ester hydrolysis.

SCHEME 3. Saponification to Epoxide 10



SCHEME 4. One-Pot Epoxidation-Bromination



efficiency. We recognized that we could run this reaction in a one-pot stepwise fashion, with dilution after complete epoxidation, followed by addition of NBS and TMG. Alternatively, all the reagents could be added at t = 0, where the epoxide would be expected to be consumed as it was produced. In the event, both approaches (see Supporting Information for full information) were successively realized using *m*CPBA, NBS and TMG (Scheme 4) to give *meta*-chlorobenzoate ethers **12** (δ_C [*C*Br] 53.5 ppm) and **13** (δ_C [*C*Br] 50.4 ppm).

Conclusion

In conclusion, we have extended the intramolecular bromonium ion-assisted epoxide ring-opening method first reported by Davies and Thomas, and more recently by Jamison and McDonald, to allow the incorporation of an added external nucleophile. In exploring such systems there is an additional inherent selectivity question—whether the added external nucleophile will attack directly the bromonium ion of the original olefin or whether the formation of an oxonium ion followed by its trapping will predominate. Using NBS and a catalytic quantity of TMG allowed the use of aliphatic and aromatic carboxylic acids to function as nucleophiles as desired, with the trapping of the presumed oxonium ion favored at high dilution. Alcohols and water could also function as the nucleophile when used directly as solvents (in conjunction with NBS) to trap the presumed oxonium in high yield regardless of the concentration. Halides (using TMSCl, LiCl or Br_2) could also be incorporated in high yields. These results demonstrate that the intramolecular bromonium ion-assisted epoxide ring-opening is a favorable and high-yielding process that can occur with a variety of added external nucleophiles. This pathway can be favored over direct attack of the external nucleophile on the bromonium ion. However, the regiochemistry of the nucleophilic capture on the oxonium ion is not highly selective and remains essentially unperturbed by the nature of the solvent or of the nucleophile. Finally, we have also demonstrated herein the value of halide-induced isotopic NMR shifts in unambiguously identifying chloride and bromide-bearing carbons, thus aiding structure elucidation in general.

Experimental Section

Representative Procedure for Bromonium Ion-Assisted Epoxide Ring-Opening with Acetic Acid as the Added External Nucleophile. To a solution of epoxyalkene **1** (100 mg, 0.80 mmol) in CH_2Cl_2 (3.6 mL) was added TMG (0.92 mg, 0.008 mmol, 1 mol %), acetic acid (0.05 mL, 1.6 mmol) and NBS (286 mg, 1.6 mmol). The mixture was stirred for 1 h at room temperature, diluted with CH_2Cl_2 (20 mL) and quenched with an aqueous solution of Na_2SO_3 (10%, 20 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated in vacuo to afford the crude material. Column chromatography eluting with petroleum ether/EtOAc (9:1 to 8:2) afforded first a 1:1 mixture of the two cyclic ethers **2** and **3** (90 mg, 43%), second, epoxide **5** (27 mg, 13%) and third, epoxide **4** (54 mg, 26%). Authentic samples of **2** and **3** were prepared from alcohols **6g** and **7g** respectively (see Supporting Information).[24]

(**1*R**,2*R**,5*S**,6*S**)-5-Bromo-9-oxabicyclo[4.2.1]nonan-2-yl Acetate (2).** Colorless oil: R_f (PE/EtOAc 8:2) 0.36; IR (neat) 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.15 (ddd, J = 3.8, 4.9, 7.4, 1H), 4.74−4.65 (m, 1H), 4.62 (ddd, J = 2.9, 4.6, 7.5, 1H), 4.20 (ddd, J = 4.9, 7.6, 9.7, 1H), 2.32−2.23 (m, 1H), 2.20−2.09 (m, 3H), 2.08 (s, 3H), 2.07−1.89 (m, 3H), 1.83−1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 82.7, 78.3, 73.3, 53.7, 29.8, 29.3, 26.1, 25.9, 21.1; MS (CI^+, NH_3) m/z 282, 280 $(M + NH_4)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_{10}H_{19}NO_3{}^{79}Br$ $(M + NH_4)^+$ 280.0548, found 280.0552.

(**1*R**,2*R**,5*R**,6*R**)-6-Bromo-9-oxabicyclo[3.3.1]nonan-2-yl Acetate (3).** Colorless oil: R_f (PE/EtOAc 8:2) 0.36; IR (neat) 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.12 (dt, J = 6.0, 11.8, 1H), 4.45 (dt, J = 5.6, 12.7, 1H), 3.96 (dt, J = 5.5, 10.7, 2H), 2.54−2.44 (m, 1H), 2.38 (ddd, J = 6.4, 12.9, 19.6, 1H), 2.29−2.20 (m, 1H), 2.07 (s, 3H), 2.10−1.85 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 70.3, 69.7, 66.5, 50.6, 31.1, 25.6, 25.1, 23.1, 21.2; MS (CI^+, NH_3) m/z 282, 280 $(M + NH_4)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_{10}H_{19}NO_3{}^{79}Br$ $(M + NH_4)^+$ 280.0548, found 280.0552.

(**1*S**,4*S**,5*S**,8*R**)-5-Bromo-9-oxabicyclo[6.1.0]nonan-4-yl Acetate (4).** Colorless oil: R_f (PE/EtOAc 9:1) 0.14; IR (neat) 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.24 (dt, J = 3.8, 8.4, 1H), 4.61 (ddd, J = 3.4, 6.8, 8.4, 1H), 3.04−2.95 (m, 2H), 2.32−2.14 (m, 5H), 2.08 (s, 3H), 1.96−1.79 (m, 1H), 1.76−1.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 73.1, 55.4, 55.2, 51.0, 29.6, 28.6, 24.1, 23.5, 21.1; MS (CI^+, NH_3) m/z 282, 280 $(M + NH_4)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_{10}H_{16}O_3{}^{79}Br$ $(M + H)^+$ 263.0283, found 263.0284.

(**1*S**,4*R**,5*R**,8*R**)-5-Bromo-9-oxabicyclo[6.1.0]nonan-4-yl Acetate (5).** Colorless oil: R_f (PE/EtOAc 9:1) 0.18; IR (neat) 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.24 (td, J = 3.4, 9.1, 1H), 4.42 (ddd, J = 4.0, 4.9, 8.9, 1H), 3.17 (dt, J = 4.3, 7.3, 1H), 3.10 (dt, J = 4.5, 9.6, 1H), 2.50−2.34 (m, 2H), 2.29−2.14 (m, 3H), 2.11 (s, 3H), 1.91−1.73 (m, 2H), 1.62−1.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 73.2, 55.5, 54.6, 53.7, 31.8, 27.9, 25.2, 23.3, 21.0; MS (CI^+, NH_3) m/z 282, 280 $(M + NH_4)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_{10}H_{16}O_3{}^{79}Br$ $(M + H)^+$ 263.0283, found 263.0285.

Benzoic Acid. Following the representative procedure (above) using benzoic acid as the added external nucleophile according to the conditions recorded in Table 2, entry 2. The crude mixture was purified by column chromatography eluting with petroleum ether/EtOAc (9:1 to 8:2) to give first, an inseparable mixture of the cyclic ether benzoates **6a** and **7a**, second epoxide **8a**, and third, epoxide **9a**. Authentic samples of **6a** and **7a** were prepared from alcohols **6g** and **7g** respectively (see Supporting Information).[24]

(24) Tetrafluorobenzoates **6c** and **7c** could be separated by HPLC and individually saponified to give pure samples of each of alcohols **6g** and **7g** (see Supporting Information).

(1*R,2*R**,5*S**,6*S**)-5-Bromo-9-oxabicyclo[4.2.1]nonan-2-yl Benzoate (6a).** Colorless oil: R_f (PE/EtOAc 9:1) 0.72; IR (neat) 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08−8.03 (m, 2H), 7.63−7.59 (m, 1H), 7.50−7.47 (m, 2H), 5.46−5.42 (m, 1H), 4.85−4.80 (m, 1H), 4.69−4.65 (m, 1H), 4.26 (dt, J = 5.0, 10.0, 1H), 2.37−1.91 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 133.2, 130.0, 129.6, 128.5, 82.9, 78.4, 73.8, 53.6, 29.8, 29.5, 26.5, 25.8; MS (CI^+, NH_3) m/z 344, 342 $(M + NH_4)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_{15}H_{21}NO_3{}^{79}Br$ $(M + NH_4)^+$ 342.0705, found 342.0706.

(1*R,2*R**,5*R**,6*R**)-6-Bromo-9-oxabicyclo[3.3.1]nonan-2-yl Benzoate (7a).** Colorless oil: R_f (PE/EtOAc 9:1) 0.73; IR (neat) 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12−8.00 (m, 2H), 7.60 (app t, J = 7.4, 1H), 7.48 (app t, J = 7.7, 2H), 5.48−5.35 (m, 1H), 4.51 (dt, J = 5.6, 12.7, 1H), 4.17−4.12 (m, 1H), 4.02 (app t, J = 4.9, 1H), 2.63−2.44 (m, 2H), 2.38−2.27 (m, 1H), 2.25−2.02 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 133.2, 130.0, 129.6, 128.5, 70.7, 69.8, 66.7, 50.6, 31.2, 25.9, 25.2, 23.2; MS (CI^+, NH_3) m/z 344, 342 $(M + NH_4)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_{15}H_{18}O_3{}^{79}Br$ $(M + H)^+$ 325.0439, found 325.0439.

(1*S,4*S**,5*S**,8*R**)-5-Bromo-9-oxabicyclo[6.1.0]nonan-4-yl Benzoate (8a).** White solid: mp 113−115 °C; R_f (PE/EtOAc 9:1) 0.20; IR (neat) 1704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06−8.00 (m, 2H), 7.65−7.57 (m, 1H), 7.51−7.45 (m, 2H), 5.59 (ddd, J = 3.3, 4.2, 7.9, 1H), 4.82 (ddd, J = 3.2, 6.1, 8.9, 1H), 3.21 (dt, J = 4.0, 9.8, 1H), 3.15 (dt, J = 4.3, 9.9, 1H), 2.43 (ddd, J = 4.4, 8.7, 15.8, 1H), 2.32−2.17 (m, 3H), 2.16−1.96 (m, 2H), 1.85−1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 133.5, 129.6, 128.7, 73.5, 55.6, 55.5, 50.6, 29.0, 28.6, 23.8, 23.6; MS (CI^+, NH_3) m/z 344, 342 $(M + NH_4)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_{15}H_{18}O_3{}^{79}Br$ $(M + H)^+$ 325.0439, found 325.0445.

(1*S,4*R**,5*R**,8*R**)-5-Bromo-9-oxabicyclo[6.1.0]nonan-4-yl Benzoate (9a).** White solid: mp 73−74 °C; R_f (PE/EtOAc 9:1) 0.16; IR (neat) 1711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, J = 1.2, 8.3, 2H), 7.64−7.58 (m, 1H), 7.50−7.45 (m, 2H), 5.52 (td, J = 3.2, 8.6, 1H), 4.64 (dt, J = 4.4, 8.7, 1H), 3.23 (dt, J = 4.2, 8.0, 1H), 3.17 (dt, J = 4.6, 9.4, 1H), 2.56−2.35 (m, 3H), 2.34−2.22 (m, 2H), 2.07−1.96 (m, 1H), 1.91−1.80 (m, 1H), 1.74−1.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 133.5, 129.7, 128.5, 73.7, 55.7, 54.8, 52.5, 31.6, 27.7, 25.2, 23.2; MS (CI^+, NH_3) m/z 344, 342 $(M + NH_4)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_{15}H_{18}O_3{}^{79}Br$ $(M + H)^+$ 325.0439, found 325.0439.

***p*-Nitrobenzoic Acid.** Following the representative procedure (above) using *p*-nitrobenzoic acid as the added external nucleophile according to the conditions recorded in Table 2, entry 3. The crude mixture was purified by column chromatography eluting with petroleum ether/EtOAc (9:1 to 8:2) to give first [3.3.1]bicycloether 4-nitrobenzoate **7b**, second, [4.2.1]bicycloether 4-nitrobenzoate **6b**, third epoxide **8b**, and fourth, epoxide **9b**.

(1*R,2*R**,5*S**,6*S**)-5-Bromo-9-oxabicyclo[4.2.1]nonan-2-yl 4-Nitrobenzoate (6b).** White solid: mp 85 °C; R_f (PE/EtOAc 8:2) 0.43; IR (neat) 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38−8.30 (m, 2H), 8.26−8.18 (m, 2H), 5.47 (ddd, J = 3.9, 4.5, 7.8, 1H), 4.84 (td, J = 2.8, 8.5, 1H), 4.69 (ddd, J = 2.5, 4.8, 7.5, 1H), 4.31−4.22 (m, 1H), 2.41−2.32 (m, 1H), 2.29−2.22 (m, 3H), 2.48−2.03 (m, 3H), 2.02−1.93 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 150.6, 135.3, 130.7, 123.6, 82.8, 78.1, 75.0, 53.2, 29.8, 29.3, 26.4, 25.9; MS (CI^+, NH_3) m/z 389, 387 $(M + NH_4)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_{15}H_{20}N_2O_5{}^{79}Br$ $(M + H)^+$ 387.0556, found 387.0558.

(1*R,2*R**,5*R**,6*R**)-6-Bromo-9-oxabicyclo[3.3.1]nonan-2-yl 4-Nitrobenzoate (7b).** White solid: mp 116 °C; R_f (PE/EtOAc 8:2) 0.47; IR (neat) 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37−8.29 (m, 2H), 8.26−8.18 (m, 2H), 5.44 (dt, J = 5.9, 10.5, 1H), 4.50 (dt, J = 5.6, 11.8, 1H), 4.16 (app t, J = 5.7, 1H), 4.03 (app t, J = 5.0, 1H), 2.66−2.57 (m, 1H), 2.55−2.43 (m, 1H), 2.39−2.30 (m, 1H), 2.29−2.05 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 150.7, 135.3, 130.7, 123.6, 72.0, 69.8, 66.4, 50.1, 31.1, 25.8, 25.1, 23.1; MS (CI^+, NH_3) m/z 389, 387 $(M + NH_4)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_{15}H_{20}N_2O_5{}^{79}Br$ $(M + NH_4)^+$ 387.0569, found 387.0566.

(1*S,4*S**,5*S**,8*R**)-5-Bromo-9-oxabicyclo[6.1.0]nonan-4-yl 4-Nitrobenzoate (8b).** White solid: mp 150 °C; R_f (PE/EtOAc 8:2) 0.33; IR (neat) 1708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37−8.31 (m, 2H), 8.25−8.20 (m, 2H), 5.56 (dt, J = 3.9, 8.2, 1H), 4.83−4.70 (m, 1H), 3.18 (dt, J = 4.2, 9.1, 1H), 3.12 (dt, J = 4.2, 10.0, 1H), 2.43 (ddd, J = 4.3, 8.9, 15.7, 1H), 2.34−2.14 (m, 4H), 2.10−1.98 (m, 1H), 1.88−1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 150.8, 135.0, 130.7, 123.8, 75.0, 55.2, 55.1, 50.5, 29.9, 28.8, 24.2, 23.5; MS (CI^+, NH_3) m/z 389, 387 $(M + NH_4)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_{15}H_{20}N_2O_5{}^{79}Br$ $(M + H)^+$ 387.0556, found 387.0570.

(1*S,4*R**,5*R**,8*R**)-5-Bromo-9-oxabicyclo[6.1.0]nonan-4-yl 4-Nitrobenzoate (9b).** White solid: mp 105 °C; R_f (PE/EtOAc 8:2) 0.25; IR (neat) 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37−8.30 (m, 2H), 8.27−8.21 (m, 2H), 5.51 (td, J = 3.4, 9.3, 1H), 4.55 (ddd, J = 3.8, 5.2, 9.0, 1H), 3.23 (dt, J = 4.3, 8.5, 1H), 3.17 (dt, J = 4.6, 9.8, 1H), 2.57−2.43 (m, 2H), 2.42−2.21 (m, 3H), 2.10−1.95 (m, 1H), 1.93−1.82 (m, 1H), 1.73−1.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 150.7, 135.2, 130.9, 123.7, 74.9, 55.3, 54.6, 53.5, 32.1, 28.2, 25.3, 23.4; MS (CI^+, NH_3) m/z 389, 387 $(M + NH_4)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_{15}H_{20}N_2O_5{}^{79}Br$ $(M + H)^+$ 387.0556, found 387.0558.

2,3,4,5-Tetrafluorobenzoic Acid. Following the representative procedure (above) using 2,3,4,5-tetrafluorobenzoic acid as the added external nucleophile according to the conditions recorded in Table 2, entry 5. The crude mixture was purified by column chromatography eluting with petroleum ether/EtOAc (9:1 to 8:2) to give first, a 1:1 mixture of bicycloethers **6c** and **7c**, second, epoxide **8c** and third, epoxide **9c**. The tetrafluorobenzoates **6c** and **7c** were separated using HPLC on a 25 cm Supelcosil LC-Si column (ID 21.2 mm), eluting with *n*-Hexane/EtOAc (90:10), flow rate 9 mL min^{-1}, detecting at 254 nm. R_t **7c** 14.8 min, R_t **6c** 16.8 min.

(1*R,2*R**,5*S**,6*S**)-5-Bromo-9-oxabicyclo[4.2.1]nonan-2-yl 2,3,4,5-Tetrafluorobenzoate (6c).** White solid: mp 80 °C; R_f (PE/EtOAc 9:1) 0.33; IR (neat) 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66−7.58 (m, 1H), 5.45 (dt, J = 4.2, 7.4, 1H), 4.78 (td, J = 2.9, 7.8, 1H), 4.67 (ddd, J = 7.6, 4.8, 2.6, 1H), 4.25−4.20 (m, 1H), 2.42−1.89 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) 161.4, 147.9 (dd, J = 264, 13), 146.5 (dd, J = 238, 11), 143.7 (dt, J = 261, 12), 141.5 (dt, J = 259, 14), 114.7 (br m), 113.2 (dd, J = 21, 3), 83.0, 78.0, 75.6, 53.2, 29.7, 29.4, 26.6, 25.8; MS (CI^+, NH_3) m/z 416, 414 $(M + NH_4)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_{15}H_{17}NO_3F_4{}^{79}Br$ $(M + NH_4)^+$ 414.0328, found 414.0328.

(1*R,2*R**,5*R**,6*R**)-6-Bromo-9-oxabicyclo[3.3.1]nonan-2-yl 2,3,4,5-Tetrafluorobenzoate (7c).** White solid: mp 38−40 °C; R_f (PE/EtOAc 9:1) 0.33; IR (neat) 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66−7.56 (m, 1H), 5.45−5.35 (m, 1H), 4.49 (dt, J = 5.5, 12.7, 1H), 4.13−4.08 (m, 1H), 4.00 (app t, J = 5.1, 1H), 2.62−2.53 (m, 1H), 2.50−2.40 (m, 1H), 2.36−2.28 (m, 1H), 2.25−2.15 (m, 1H), 2.15−2.02 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 147.6 (dd, J = 260, 10), 146.5 (dd, J = 249, 12), 143.5 (dt, J = 274, 16), 141.5 (dt, J = 255, 14), 114.7 (br m), 113.2 (dd, J = 21, 3), 72.4, 71.6, 69.8, 66.4, 50.2, 31.0, 25.7, 25.1, 23.1; MS (CI^+, NH_3) m/z 416, 414 $(M + NH_4)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_{15}H_{17}NO_3F_4{}^{79}Br$ $(M + NH_4)^+$ 414.0328, found 414.0331.

(1*S,4*S**,5*S**,8*R**)-5-Bromo-9-oxabicyclo[6.1.0]nonan-4-yl 2,3,4,5-Tetrafluorobenzoate (8c).** White solid: mp 45 °C; R_f (PE/EtOAc 9:1) 0.21; IR (neat) 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (tdd, J = 2.5, 6.0, 10.4, 1H), 5.57 (dt, J = 3.7, 8.4, 1H), 4.81−4.63 (m, 1H), 3.13−3.04 (m, 2H), 2.44−2.36 (m, 1H), 2.33−2.08 (m, 4H), 2.08−1.92 (m, 1H), 1.85−1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7 (dd, J = 263, 12),

146.5 (dd, J = 250, 10), 143.7 (dt, J = 262, 13), 141.3 (dt, J = 256, 13), 114.2 (br m), 113.4 (dd, J = 21,1), 75.5, 55.4, 55.0, 50.3, 29.5, 28.6, 24.1, 23.4; MS (CI^+, NH_3) m/z 416, 414 $(M + NH_4)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_{15}H_{14}O_3F_4{}^{79}Br$ $(M + H)^+$ 397.0062, found 397.0063.

(1*S,4*R**,5*R**,8*R**)-5-Bromo-9-oxabicyclo[6.1.0]nonan-4-yl 2,3,4,5-Tetrafluorobenzoate (9c).** Colorless oil: R_f (PE/EtOAc 9:1) 0.18; IR (neat) 1728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71−7.59 (m, 1H), 5.52 (td, J = 3.2, 8.8, 1H), 4.56 (dt, J = 4.4, 8.8, 1H), 3.21 (dt, J = 4.3, 7.4, 1H), 3.15 (dt, J = 4.7, 9.8, 1H), 2.56−2.21 (m, 5H), 2.07−1.98 (m, 1H), 1.91−1.79 (m, 1H), 1.72−1.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 148.0 (dd, J = 261, 9), 146.4 (dd, J = 226, 9), 144.0 (dt, J = 227, 24), 141.3 (dt, J = 237, 14), 114.4 (m), 113.3 (dd, J = 21, 2), 75.3, 55.5, 54.6, 52.5, 31.7, 29.7, 27.7, 25.0, 23.2; MS (CI^+, NH_3) m/z 399, 397 $(M + H)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_{15}H_{14}O_3F_4{}^{79}Br$ $(M + H)^+$ 397.0062, found 397.0070.

Trimethylsilylchloride. Following the representative procedure (above) using (trimethysilyl)chloride as the added external nucleophile according to the conditions recorded in Table 2, entry 6. The crude mixture was purified by column chromatography eluting with petroleum ether/EtOAc (19:1) to afford an inseparable mixture of bicyclic ethers **6d** and **7d** as a white solid. The chlorides **6d** and **7d** were separated using HPLC on a 25 cm Supelcosil LC-Si column (ID 21.2 mm), eluting with *n*-Hexane/*i*PrOH (95:5), flow rate 10 mL min^{-1}, detecting at 230 nm. R_t **6d** 41.0 min; R_t **7d** 31.0 min.

(1*S,2*S**,5*R**,6*R**)-2-Bromo-5-chloro-9-oxabicyclo[4.2.1]nonane (6d).** Colorless oil: R_f (PE/EtOAc 19:1) 0.48; ^1H NMR (500 MHz, $CDCl_3$) δ 4.62−4.58 (m, 2H), 4.31−4.25 (m, 2H), 2.44−2.35 (m, 2H), 2.25−2.18 (m, 2H), 2.18−2.00 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 82.0, 81.5, 60.4, 53.4, 32.1, 31.2, 27.4, 26.7; GC-MS (EI^+) R_t 15.2 min: m/z 242, 240, 238 ($M^{+\cdot}$); HRMS (EI^+) m/z calcd for $C_8H_{12}O^{35}Cl^{79}Br$ $(M + H)^+$ 237.9760, found 237.9755.

(1*R,2*R**,5*R**,6*R**)-2-Bromo-6-chloro-9-oxabicyclo[3.3.1]nonane (7d).** White solid: mp 43−44 °C; R_f (PE/EtOAc 19:1) 0.48; ^1H NMR (500 MHz, $CDCl_3$) δ 4.49−4.41 (m, 1H), 4.35−4.25 (m, 1H), 3.95 (app t, J = 5.5, 2H), 2.52−2.46 (m, 1H), 2.46−2.30 (m, 2H), 2.29−2.11 (m, 3H), 2.10−1.98 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.6, 69.6, 57.6, 50.3, 31.1, 30.3, 25.1, 24.9; GC-MS (EI^+) R_t 14.6 min: m/z 242, 240, 238 ($M^{+\cdot}$); HRMS (EI^+) m/z calcd for $C_8H_{12}O^{35}Cl^{79}Br$ ($M^{+\cdot}$) 237.9760, found 237.9755.

Lithium Chloride. Following the representative procedure (above) using (lithium) chloride as the added external nucleophile according to the conditions recorded in Table 2, entry 7. The crude mixture was purified by column chromatography eluting with petroleum ether/EtOAc (19:1) to afford an inseparable mixture of bicyclic ethers **6d** and **7d** as a white solid and epoxides **8d** and **9d** as an inseparable mixture.

(1*R,4*S**,5*S**,8*S**)-4-Bromo-5-chloro-9-oxabicyclo[6.1.0]nonane (8d) and (1*R**,4*R**,5*R**,8*S**)-4-bromo-5-chloro-9-oxabicyclo[6.1.0]nonane (9d).** White solid: mp 112−113 °C; R_f (PE/EtOAc 19:1) 0.32; ^1H NMR (400 MHz, $CDCl_3$) resonances for **8d** only δ 4.73−4.66 (m, 2H), 3.17 (dt, J = 3.9, 10.5, 1H), 3.10 (dt, J = 4.6, 9.5, 1H), 2.68−2.55 (m, 2H), 2.27−2.14 (m, 3H), 2.14−2.03 (m, 1H), 1.76−1.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) resonances for **8d** only: δ 60.5, 55.9, 54.9, 53.9, 31.8, 29.1, 24.0, 23.5; MS (CI^+) m/z 243, 241, 239 $(M + H)^+$; HRMS (CI^+) m/z calcd for $C_8H_{13}{}^{35}Cl^{79}BrO$ $(M + H)^+$ 238.9838, found 238.9838.

Methanol. Following the representative procedure (above) using methanol as the added nucleophile according to the conditions recorded in Table 2, entry 8. The crude mixture was purified by column chromatography eluting with petroleum ether/EtOAc (9:1 to 8:2) to give an inseparable mixture of the cyclic ethers **6e** and **7e**. Authentic samples of **6e** and **7e** were prepared from alcohols **6g** and **7g** respectively (See Supporting Information).[24]

(1*S,2*S**,5*R**,6*R**)-2-Bromo-5-methoxy-9-oxabicyclo[4.2.1]nonane (6e).** Colorless oil: R_f (PE/EtOAc 4:1) 0.60; IR (neat) 1098, 1066 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.61 (ddd, J = 2.9, 7.1, 9.1, 1H), 4.58−4.54 (m, 1H), 4.24−4.13 (m, 1H), 3.65 (ddd, J = 3.6, 5.0, 7.1, 1H), 3.30 (s, 3H), 2.34−2.21 (m, 2H), 2.12−2.03 (m, 2H), 2.03−1.89 (m, 2H), 1.86−1.71 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 82.6, 80.4, 79.4, 57.1, 54.6, 29.7, 28.4, 26.1, 25.1; MS (CI^+, NH_3) m/z 254, 252 $(M + NH_4)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_9H_{19}NO_2{}^{79}Br$ $(M + NH_4)^+$ 252.0599, found 252.0590.

(1*R,2*R**,5*R**,6*R**)-2-Bromo-6-methoxy-9-oxabicyclo[3.3.1]nonane (7e).** Colorless oil: R_f (PE/EtOAc 9:1) 0.22; IR (neat) 1127, 1103, 1082, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.46 (dt, J = 5.5, 12.7, 1H), 4.01 (app t, J = 5.6, 1H), 3.93 (app t, J = 5.5, 1H), 3.61 (dt, J = 5.9, 11.7, 1H), 3.38 (s, 3H), 2.49 (dd, J = 5.9, 14.3, 1H), 2.41−2.28 (m, 1H), 2.21 (dt, J = 6.2, 13.7, 1H), 2.12−1.90 (m, 4H), 1.85−1.67 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 77.6, 69.9, 67.3, 56.3, 51.2, 31.3, 25.7, 25.1, 23.2; MS (CI^+, NH_3) m/z 254, 252 $(M + NH_4)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_9H_{19}NO_2{}^{79}Br$ $(M + NH_4)^+$ 252.0599, found 252.0596.

Water. Following the representative procedure (above) using water as the added nucleophile according to the conditions recorded in Table 2, entries 10−12. The crude mixture was purified by column chromatography to give an inseparable mixture of the cyclic ethers **6g** and **7g**.[24]

(1*R,2*R**,5*S**,6*S**)-5-Bromo-9-oxabicyclo[4.2.1]nonan-2-ol (6g).** Colorless oil: R_f (PE/EtOAc 1:1) 0.36; IR (neat) 3379 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.60−4.50 (m, 2H), 4.22 (dt, J = 5.4, 8.3, 1H), 4.17 (dt, J = 4.9, 6.8, 1H), 2.38−2.22 (m, 2H), 2.19−1.85 (m, 5H), 1.81 (s, 1H), 1.76−1.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.1, 80.9, 71.1, 54.3, 32.2, 29.7, 26.7, 24.9; MS (CI^+, NH_3) m/z 240, 238 $(M + NH_4)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_8H_{17}NO_2{}^{79}Br$ $(M + NH_4)^+$ 238.0443, found 238.0439.

(1*R,2*R**,5*R**,6*R**)-6-Bromo-9-oxabicyclo[3.3.1]nonan-2-ol (7g).** Colorless oil: R_f (PE/EtOAc 1:1) 0.28; IR (neat) 3368 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.44 (dt, J = 5.6, 12.7, 1H), 4.06 (dt, J = 5.8, 11.6, 1H), 3.91 (app t, J = 5.3, 1H), 3.85 (app t, J = 5.8, 1H), 2.51−2.43 (m, 1H), 2.40−2.28 (m, 1H), 2.26−2.16 (m, 2H), 2.15−2.08 (m, 1H), 2.05−1.93 (m, 3H), 1.90−1.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.7, 69.6, 68.4, 51.0, 31.3, 28.6, 24.6, 23.3; MS (CI^+, NH_3) m/z 240, 238 $(M + NH_4)^+$; HRMS (CI^+, NH_3) m/z calcd for $C_8H_{17}NO_2{}^{79}Br$ $(M + NH_4)^+$ 238.0443, found 238.0434.

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Supporting Information Available: General experimental, procedure for dilution studies shown in Table 1 with ^1H NMR spectra, procedures for the saponification of tetrafluorobenzoates **6c** and **7c** to provide alcohols **6g** and **7g**, procedures for the preparation of authentic samples of **2**, **3**, **6a**, **7a**, **6e** and **7e** from alcohols **6g** and **7g**, procedure and characterizing data for bicycloethyl ethers **6f** and **7f**, procedure for saponification of tetrafluorobenzoate **9c** to bisepoxide **10**, procedures and characterizing data for the one-pot epoxidation-bromination of 1,5-cyclooctadiene **11** to give **12** and **13**, copies of ^1H and ^{13}C NMR spectra for **2**−**5**, **6a**, **7a**, **8a**, **9a**, **6b**, **7b**, **8b**, **9b**, **6c**, **7c**, **8c**, **9c**, **6d**, **7d**, **8d**, **6e**, **7e**, **6f** and **7f**, **6g**, **7g**, **10**, **12**, **13**, copies of ^{13}C NMR resonances exhibiting bromine (**2**, **3**, **4**, **6a**, **7a**, **6b**, **8b**, **6c**, **7c**, **8c**, **6d**, **7d**, **8d**, **6e**, **7e**, **8e**, **6g**, **12**, **13**) and chlorine (**6d**, **7d**)-induced isotopic shifts, and X-ray crystallographic details for **6b**, **6c**, **7b**, **7c**, **7d** and **8a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.