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The Reaction of 8-Amino-*p*-menthene Derivatives with Electrophiles

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Attempts to ring-close the nitrogen atom of 8-amino-*p*-menth-1-ene and of *N*-substituted 8-amino-*p*-menth-1-enes onto the C1–C2 double-bond carbons has led to a range of bicyclo[2.2.2] and bicyclo[3.2.1] products, together with the novel bicyclo[4.3.1]-1,3-oxazepine **9**.

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Introduction

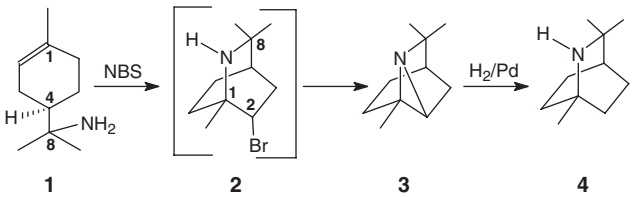
We recently discussed[1] the synthesis of 'azacineole' **4** from 8-amino-*p*-menth-1-ene **1** through the steps listed in Scheme 1. The intermediate 2-bromo bicyclic compound **2** was too unstable to isolate, and the nucleophilic nitrogen atom rapidly displaced the bromine to form aziridine **3**. While compound **3** could be readily converted into the desired bicycle **4**, we were also attracted to the possibility that the employment of less nucleophilic nitrogen substituents might enable the isolation of more stable 2-substituted azacineoles.

This approach, together with attempts to cyclize compound **1** by using mercury electrophiles, is now discussed.

Results and Discussion

There are numerous examples in the literature of the intramolecular ring closure of *N*-acyl-protected nitrogen atoms onto activated C=C double bonds.[2] In the present example we anticipated that derivatives **5a**–**5c** might, following electrophilic activation of the C=C double bond, be cyclized to structures **6** (Scheme 2). Products **6a**–**6c** were expected to be isolable since the non-nucleophilic amide would be unlikely to displace the E group. The E group and amide groups could then be modified or removed at will.

The *N*-acetyl **5a**, *N*-*tert*-butyloxycarbonyl (BOC) **5b**, and *N*-benzoyl **5c** derivatives of amine **1** were synthesized. Each compound was then reacted separately with *N*-bromosuccinimide (NBS), with greatly disparate results.

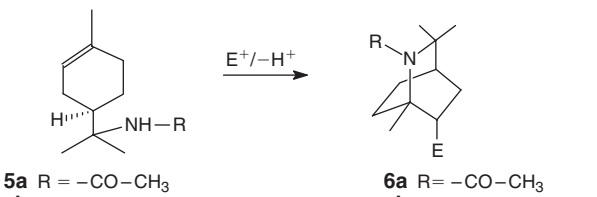


1 **2** **3** **4**

Scheme 1.

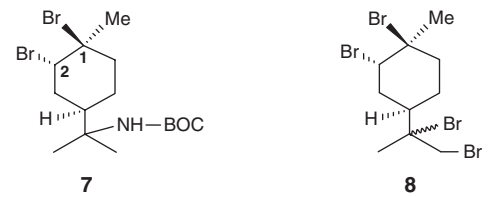
Unchanged starting material was the only isolatable compound from the attempted reaction of *N*-acetyl derivative **5a** with one equivalent of NBS in acetone. Despite the use of prolonged reaction times and refluxing solvent, no new products were observed by TLC, GC/MS, or NMR spectroscopy. The acetamide nitrogen atom was evidently not nucleophilic enough to attack any bromonium ion produced during the reaction.

The *N*-BOC derivative **5b** was reacted with NBS at room temperature for 19 h, when no further product formation was observed. A significant amount of starting material remained (determined by TLC), but at least one new compound was present. Flash chromatography resulted in significant degradation of this new product but a pure sample was collected in 14% isolated yield. The high-resolution mass spectra, NMR spectra, and microanalysis results of this new compound were consistent with structure **7**. Evidently, the double bond of compound **5b** reacted with NBS to give a bromonium ion, which was not attacked by any nucleophile until bromine atoms in the reaction mixture were converted into bromide



5a R = −CO−CH_3
b R = −CO−$OC(CH_3)_3$ (BOC)
c R = −CO−Ph
d R = −CH_2−Ph

6a R= −CO−CH_3
b R= −CO−$OC(CH_3)_3$
c R= −CO−Ph
d R= −CH_2−Ph



7 **8**

Scheme 2.

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ions or molecular bromine. The *trans* diaxial stereochemistry for the two bromine atoms was obtained by comparison with the NMR spectra of limonene tetrabromides **8**.[3–5] In both compounds **7** and **8** (two diastereomers) the ^{1}H NMR signal for H2 exists as a doublet of doublets at δ 4.7 ($J \approx 3.5$ and 3.0 Hz).

The maximum yield possible for the formation of compound **7** is 50% when equimolar amounts of starting **5b** and NBS are employed. A compound with an identical mass spectrum to compound **7** was the major product from the reaction of a sample of compound **5b** with bromine in dichloromethane.

It is interesting to note that the double bond in the *N*-BOC case, **5b**, was brominated while under identical conditions the double bond of the *N*-acetyl derivative **5a** was completely inert. In the former case, breakdown of the BOC group under the reaction conditions must presumably allow production of bromide ions.

In the *N*-benzoyl case, **5c**, the course of the NBS reaction was again entirely different. Reaction with one equivalent of NBS at room temperature led to complete loss of starting material after only four hours. There was no evidence for dibromination of the C1–C2 double bond of the starting material. The only isolable product after chromatography was the bicyclic 4,5,6,7-tetrahydro-1,3-oxazepine derivative **9** in 32% yield. The compound gave crystals from methanol and was somewhat unstable, as befits a tertiary bromide. The compound showed NMR spectra consistent with a carbon carrying a tertiary bromine, and a proton geminal to the oxygen attachment. This appears to be the first reported compound to contain a 1,3-oxazepine moiety as part of a bicyclo[4.3.1]decane ring system. Both the structure and absolute configuration were confirmed by X-ray crystallography (Fig. 1). These data may suggest some delocalization about the O1—C11—N1 region of the molecule, with bond lengths of 1.25 and 1.37 Å, respectively, for the C11—N1 and C11—O1 bonds, while the dihedral angle (N1—C11—C12—C17 −9.6(7)°) indicates that the OCN group is almost coplanar with the phenyl ring. The only analogous oxazepine for which an X-ray structure is available[6] is a less sterically constrained compound carrying a stabilizing cyano group rather than the phenyl group on the equivalent C11 atom, and shows a shorter 1.33 Å C—O bond.

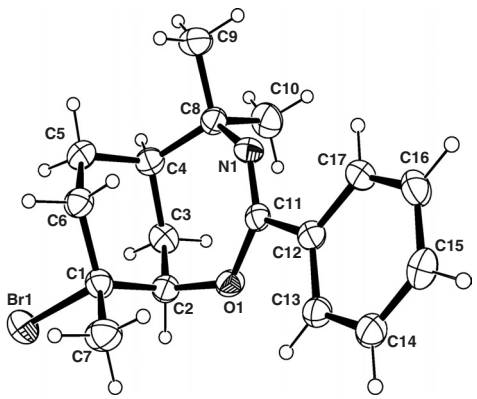


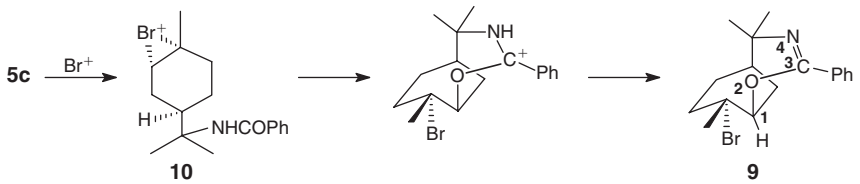
Fig. 1. The X-ray structure of the bicyclic 1,3-oxazepine derivative **9**.

The crystalline material was optically active and had $[\alpha]_D$ −54° at 25°C. The starting limonene used in the synthesis of the compound was >98% the *R*-(+) enantiomer, and hence the product is expected to be enantiomerically pure.

1,3-Oxazepines with a C–N double bond identically placed to that of compound **9** are known to be stabilized if a phenyl or cyano group is attached to the carbon atom between the oxygen and the nitrogen,[7] allowing delocalization of electrons to occur. Examples do not exist where this attached group is a methyl or a *t*-butyl ether, and presumably such products are unstable, as is suggested by Avenosa et al.[8] in work on simpler 1,3-oxazines.

A mechanism leading to compound **9** involves nucleophilic attack by the oxygen atom of the carbonyl group to the back of the C2—Br bond of the bromonium ion **10** (Scheme 3). Of the possible ring closures available to this ion **10** there are two products, structures **11** and **12** (Scheme 4), that could be formed by nitrogen attack, and two products that could be formed by oxygen attack, structures **9** and the less-likely structure **13** with an eight-membered ring. To study the energetics of these pathways, the heats of formation for the six possible transition states (there are two possibilities for each of the nitrogen ring closures depending on whether or not the carbonyl C—O bond points in the same general direction as the C—Br bond) were calculated for the gas phase using each of the three MOPAC (a semi-empirical molecular orbital program, version 6.00)[9,10] force fields; MNDO, AM1, and PM3. However calculated energy differences between the six possible reaction pathways were small, and we are forced to conclude that solvation effects must be playing a major part in favouring the route leading to the observed product **9**. (Calculations with energies and input and output structures are available from the authors.)

For structure **11**, superficially the anticipated product from the cyclization of starting material **5c**, Dreiding models indicate an extremely hindered situation where the volume



Scheme 3.

occupied by the C7, C9, and C10 methyl groups forces the N─CO bond to rotate so that the protons on the phenyl ring are no longer in the same space as the methyl groups. This rotation results in the loss of delocalization across the amide group. The MOPAC results supported this view, with the minimal-energy conformer for structure **11** having the planes of the C8─N─C1 atoms and the carbonyl–phenyl system at roughly 90° to each other.

In a further exploration, compound **1** was treated with NBS in the presence of perchloric acid, following the rationale of Yardley and Rees[11] who argued that the bromonium ion formed under aqueous acidic conditions would not be attacked by the protonated amine, allowing, instead, the formation of a bromohydrin. Subsequent basification might then allow displacement of the bromine atom by the amino group, leading to structures such as **14** (Scheme 4). In the event, the only isolated product was epoxide **15**, formed by alkaline treatment of a corresponding bromohydrin. Compound **15**, although a simple amino epoxy-*p*-menthane, appears to be a new compound. Its stereochemistry was obtained by comparison of NMR spectra with those of other 1,2-epoxy-*p*-menthanes.[12–14] Compound **15** displays H2 as a doublet (J 5.3 Hz) at δ 2.97, comparable with the literature and different from the alternate α-epoxide stereochemistry where obvious doublets of doublets ($J \approx 2$, ≈ 2 Hz) are observed. The stereochemistry in compound **15** does not allow subsequent S_N2 displacement of the epoxide group by the amino nitrogen.

In an attempt to gain further insight into the ring closure of the various *N*-protected starting materials, amine **1** and its derivatives **5** were then examined with mercuric acetate. The direct reaction of mercuric acetate with unprotected amine **1** was very slow, with considerable reversion back to starting materials. Demercuration afforded recovered starting amine **1** (35%), aziridine **3** (30%), and unstable acetate **16**[1] (26%).

The reaction of compound **1** with mercuric trifluoroacetate, followed by hydride reduction under alkaline conditions, proved cleaner and faster. Only 4% of starting material **1** was recovered, with aziridine **3** (12%) and a new crystalline alcohol **17** (81%) predominating. Compound **17**, a racemate, is assumed to form by a Treibs-type mechanism[15–19] involving reversible allylic rearrangement about carbons 2, 1, and 6. This compound is also a new product, and its structure was verified by X-ray crystallography (Fig. 2). This determination revealed the presence of one molecule of strongly hydrogen-bonded water per product molecule in the unit cell, where it is of interest that the lone pair of electrons on the nitrogen atom are not directly involved in the hydrogen bonding (Fig. 3).

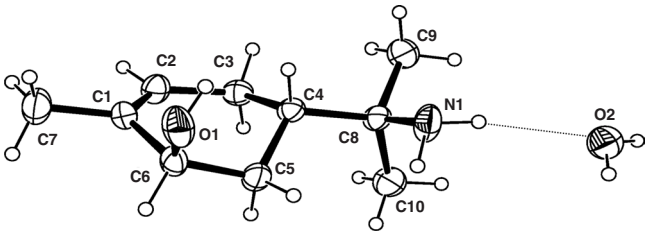


Fig. 2. X-Ray structure of compound **17**.

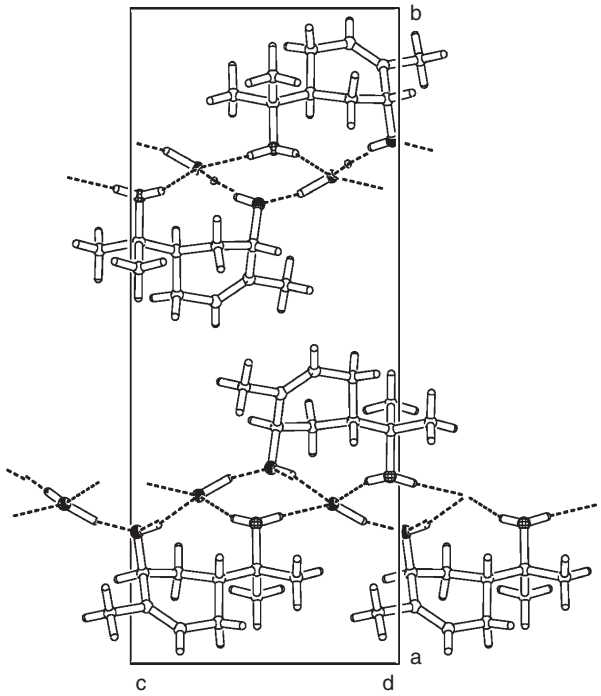
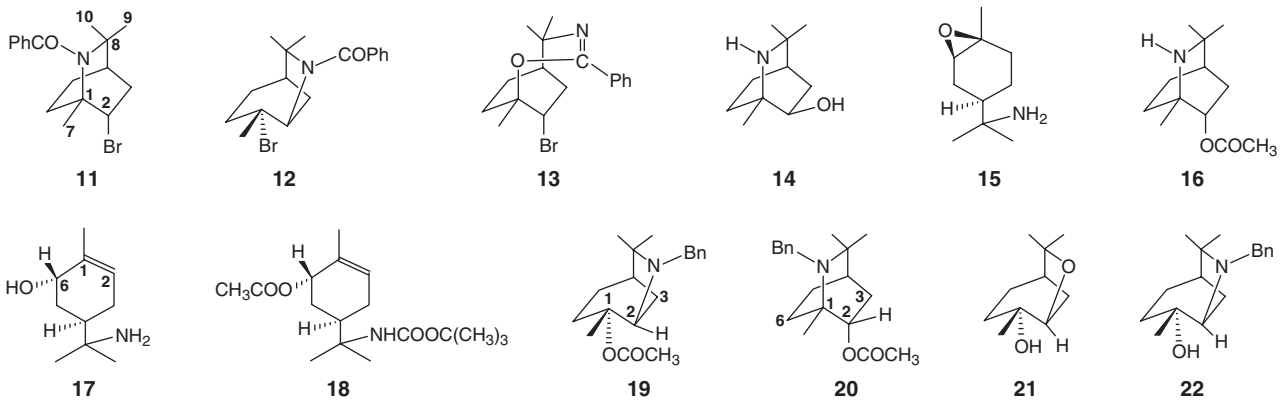


Fig. 3. The unit cell of allylic alcohol **17**, viewed along the *a* axis, showing hydrogen-bonding interactions.



Scheme 4.

The lack of formation of a trifluoroacetate corresponding to acetate **16** in this reaction is presumably a reflection of the poor nucleophilic properties of the trifluoroacetate anion.

The mercuration–demercuration of *N*-acetyl derivative **5a** with mercuric acetate led to a complete recovery of unchanged starting material.

The *N*-BOC compound **5b** did react with mercuric acetate, although not to completion and not to give a ring-closed product. The isolated crystalline product was acetate **18** (Scheme 4). The racemic nature of this compound, which is presumably also formed by a Triebs-type pathway, was confirmed by X-ray crystallography (Fig. 4).

Mercuration–demercuration of *N*-benzoyl derivative **5c** with mercuric acetate under identical conditions to those applied to the *N*-BOC derivative led only to complete recovery of starting material. No Treibs-type reaction was observed.

The *N*-benzyl compound **5d** reacted with mercuric acetate in dichloromethane to provide, in 88% isolated yield after reduction of the intermediate organomercurial, a ring-closed product characterized as *N*-benzyl-2,8-azacineole-1-acetate **19**. Compound **19** was distinguished from the other potential product, isomeric structure **20** (Scheme 4), on the basis of the H2 coupling pattern in the ^{1}H NMR spectrum. The signal for H2 of compound **19** shows a doublet at δ 3.57, with J 6.8 Hz to one H3, and with a coupling of $J \approx 0$ Hz to the other adjacent C3 proton with which it makes a torsion angle of approximately 90°. This pattern is similar to that shown by pinol **21**[20] where H2 provides a doublet at δ 3.82, with J 5 and 0 Hz to the two adjacent C3 protons. The alternate bicyclo[2.2.2]structure **20** is expected, from many examples,[1,21,22] to provide H2 as a doublet of doublets of doublets, with observable couplings to two H3 and long-range W to H6.

The tertiary nature of the acetate group in structure **19** was chemically confirmed by reduction of the compound with lithium aluminium hydride in ether to the alcohol **22** in 96% yield. This tertiary alcohol **22** was resistant to normal oxidation.

A mechanism for the formation of compound **19** is provided in Scheme 5, where the leaving group L is unclear but is probably derived from an HgH substituent.[23] It is then of interest to compare the attack of acetate anion upon the two aziridine rings present in compounds **3** and **23**, where the first compound **3** leads to the isolated [2.2.2]bicyclo product **16**,[1] while the benzyl derivative **23** provides the alternate [3.2.1] derivative **19**. Attack of a nucleophile might be expected to be faster at the less-hindered C2 position of the aziridine **23** leading to the kinetic [2.2.2]bicyclo product **24** (Scheme 6). However this un-isolated material is labile, reverting back to structure **23**. Slower attack at the more-hindered C1 end of aziridine **23** leads to the thermodynamic [3.2.1] product **19**. Protonation is not required in this sequence, which proceeds rapidly under alkaline conditions. In contrast, aziridine **3** requires protonation to become activated as salt **25** before nucleophilic ring opening occurs (Scheme 7). Kinetic attack at C2 affords salt **26**, in which the protonated nitrogen is not nucleophilic enough to displace the acetate group, so under these conditions the product **26** is not in equilibrium with

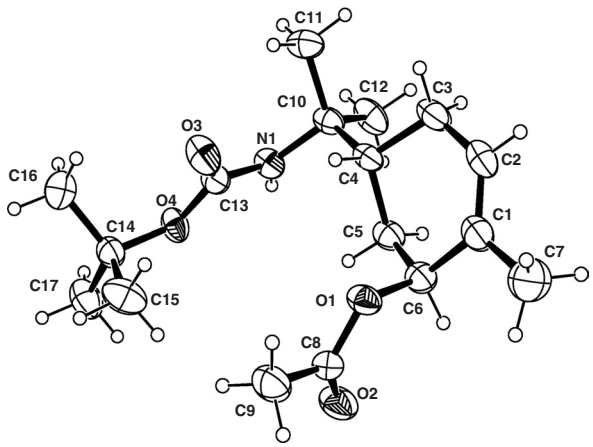
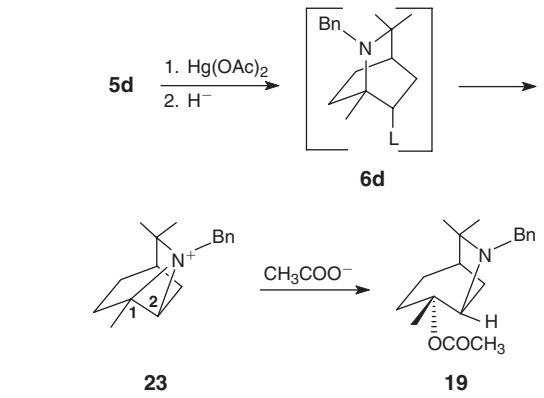
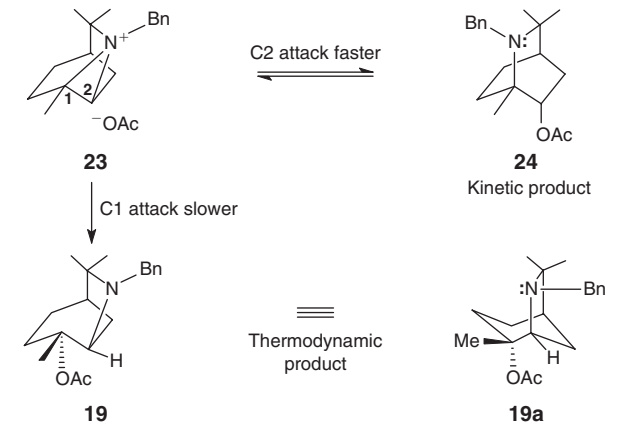


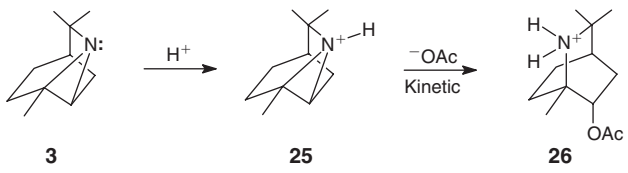
Fig. 4. X-Ray structure of compound **18**.



Scheme 5.



Scheme 6.



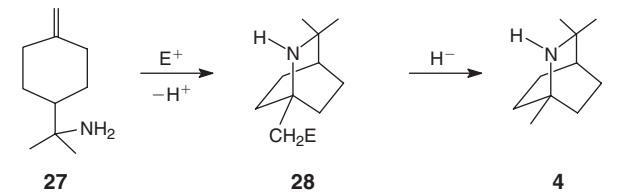
Scheme 7.

starting material **3**. In summary, structures **23** and **24** can equilibrate under alkaline conditions, whereas under these conditions structure **3** does not convert into acetate **26**.

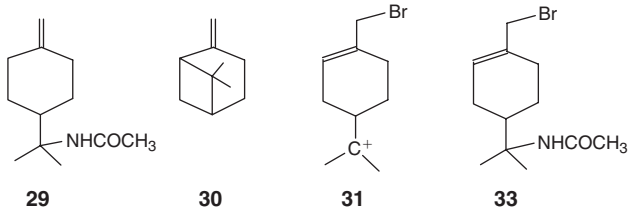
MOPAC calculations (gas phase) did not provide clear evidence for the lower heat of formation of the [3.2.1] bicycles (e.g., structure **19**) over the [2.2.2] system (e.g., **24**), but they do allow the prediction of conformer **19a** to be the most stable arrangement available to compound **19**.

The above results did not lead to a useful synthesis of 1,8-azacineole **4**, partly because of participation at the C2 position. A modified route starting from 8-amino-*p*-menth-1(7)-ene **27** might lead to improvements since reaction of amine **27** with an electrophile (Scheme 8) would give a bicyclic intermediate **28** uncomplicated by the possibility of further displacement to give an aziridine skeleton, and removal of the E group in a subsequent step should then be facile.

Amine **27** is an unknown compound. However, the acetamide derivative **29**, with the required exocyclic double bond and a suitably placed nitrogen atom, is available[24] from β-pinene **30** in a Ritter-type reaction by using NBS and trapping the resultant carbocation **31** with acetonitrile to afford



Scheme 8.



Scheme 9.

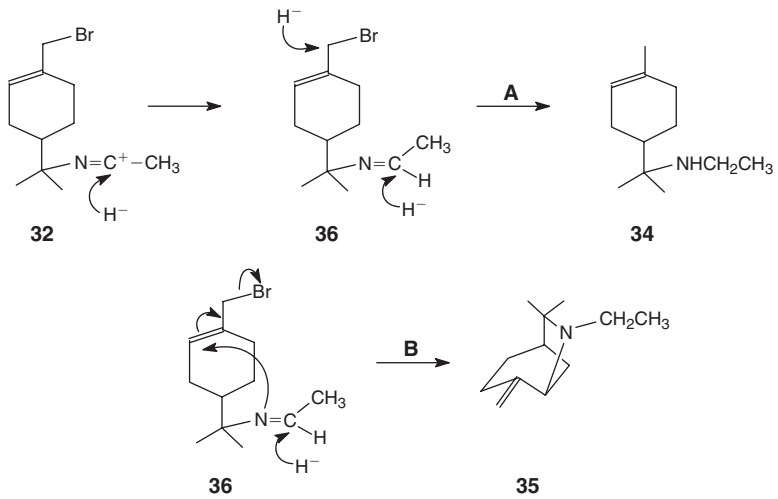
cation **32**. Subsequent aqueous workup to give amide **33**, followed by removal of the bromine from this surprisingly stable allylic bromide with zinc powder in acetic acid affords acetamide **29** (Scheme 9). We have now employed numerous reagents in an attempt to hydrolyze the acetamide **29**, but the compound proved to be stable under non-acidic conditions and amine **27** could not be successfully produced. Hydrolysis of compound **29** did occur in 10% aqueous sulfuric acid, but these conditions were then too harsh to allow the survival of the resulting amine **27**, containing a protonated amino group attached to a tertiary carbon atom, and ammonia was lost from the product to leave a mixture of isomeric monoterpene dienes. Thus we have not obtained compound **27** by this route.

We also attempted to trap cation **32** with hydride, with interesting results. Two new compounds, ethylamine **34** and the [3.2.1] bicycle **35** were produced (Scheme 10). In pathway A, two equivalents of hydride add to imine **36**, providing structure **34**. The alternate pathway B features the addition of one equivalent of hydride to imine **36** with a concomitant cyclization (either concerted or in discrete steps) to generate bicyclic amine **35**. Pathways A and B compete with each other. When excess hydride (3.0 equivalents of $NaBH_4$) was used, the product ratio of **34** to **35** was 85 : 15. When less hydride was added (0.5 equivalents of $NaBH_4$), the product ratio of **34** to **35** was 10 : 90.

All these attempts failed to provide the desired bicyclo[2.2.2]-1,8-azacineole skeleton **4**, and studies to explore the ring closures of other *N*-substituted derivatives have been abandoned at this stage.

Experimental

^1H and ^{13}C NMR spectra in $CDCl_3$ solution were recorded using either a Bruker AMX400 or AV400 spectrometer. Multiplicities for some obscured and overlapped ^1H peaks were obtained from ^1H–^1H correlation spectroscopy (COSY); where the magnitude of the coupling constants could not be measured, there are indicated in the spectral data as '?'. ^{13}C multiplicities were assigned by the distortionless enhancement by polarization transfer (DEPT) pulse sequence. Mass spectra were recorded upon a Hewlett Packard MSD5970 spectrometer using a GC inlet and BP5 column. High-resolution mass spectra were



Scheme 10.

recorded on both Finnigan 2001 FT-MS and Kratos MS25RFA instruments. Infrared spectra were measured using a Perkin–Elmer 1600 series FT-IR spectrometer with NaCl disks. GC analyses were performed upon a BP5 capillary column with flame ionization detection in a Varian 3300 instrument. Flash column chromatography was performed using Merck silica, grade 60, and distilled solvents. New compounds were refined to >99% (by NMR and GC) purity and analyzed by microanalysis and/or high-resolution mass spectrometry.

Acetamide ***5a***

Amine **1**,[1] in ether containing triethylamine, was acetylated with acetic anhydride to give *(*R*)*-N-*{1-methyl-1-[4-methylcyclohex-3-en-1-yl]ethyl}acetamide [(*R*)-8-acetamido*-p-*menth-1-ene]* **5a** (95%) as colourless prisms, mp 113–114°C (lit.[25] 111°C) (Found: C 73.8, H 11.2, N 7.3. Calc. for $C_{12}H_{21}NO$: C 73.8, H 10.8, N 7.2%). NMR spectra were consistent with the literature[25,26] and provided extra information. δ_H 5.32 (m, $W_{h/2}$ 12, H2), 5.28 (br s, $W_{h/2}$ 10, NH), 2.08 (dddd, *J* 12.6, 12, 5, 2.6, H4), 2.02–1.89 (3H, m, 1 × H6 and 2 × H3), 1.88 (3H, s, H12), 1.78–1.66 (2H, m, $H5_{eq}$ and 1 × H6), 1.59 (3H, br s, H7), 1.26 and 1.23 (2 × 3H, s, H9 and H10), 1.19 (dddd, *J* 12, 12, 12, 5.3, $H5_{ax}$). δ_C see Table 1. ν_{max} (Nujol)/cm^{-1} 3268, 3087, 2723, 1641, 1565, 1314, 1296, 1194, 1158, 1032, 965, 916, 800, 721. *m/z* (GCMS) 195 (M, 9%), 180 (M − 15, 1), 138 (7), 137 (11), 136 (95), 122 (12), 121 (100), 107 (16), 101 (19), 100 (55), 94 (13), 93 (81), 92 (17), 91 (24), 86 (15), 79 (32), 77 (25).

Carbamate ***5b***

Amine **1**, in dichloromethane containing pyridine, was treated with di-*tert*-butyl dicarbonate to afford, after flash chromatography over silica (3% diethyl ether, 97% hexane), a viscous oil. Prolonged exposure to high vacuum gave analytically pure *(*R*)*-tert-*butyl 1-methyl-1-[4-methylcyclohex-3-en-1-yl]ethylcarbamate [(*R*)-N-BOC-8-amino-*p-*menth-1-ene]* **5b** (73%) (Found: C 71.0, H 11.2, N 5.3. $C_{15}H_{27}NO_2$ requires C 71.1, H 10.7, N 5.5%). δ_H 5.34 (m, $W_{h/2}$ 11, H2), 4.40 (br s, $W_{h/2}$ 13, NH), 2.04–1.88 (4H, m, 2 × H3, H4 and 1 × H6), 1.79–1.72 (2H, m, 1 × H5 and 1 × H6), 1.60 (3H, br s, H7), 1.39 (9H, s, *t*-butyl), 1.25–1.16 (m, one H5), 1.22 and 1.18 (2 × 3H s, H9 and H10). δ_C see Table 1. ν_{max} (neat)/cm^{-1} 3452, 3362, 2972, 2925, 2835, 1722, 1559, 1497, 1455, 1388, 1364, 1308, 1252, 1224, 1173, 1118, 1070, 1034, 1023, 993, 938, 915, 884, 844, 799, 781, 759, 745. *m/z* (GCMS) 197 (M − 56, 3%), 182 (1), 180 (1), 158 (11), 137 (12), 136 (39), 121 (25), 95 (12), 93 (26), 92 (11), 91 (11), 81 (21), 79 (21), 77 (15), 58 (85), 57 (100).

Benzamide ***5c***

Amine **6** (766 mg, 5 mmol), in dichloromethane containing pyridine, was treated with benzoyl chloride to provide a colourless powder (92%) giving long fine needles of *(*R*)*-N-*[1-methyl-1-(4-methylcyclohex-3-en-1-yl)ethyl]benzamide [(*R*)-N-(*p-*menth-1-en-8-yl)benzamide]* **5c**, mp 134–135°C (from benzene) (lit.[27] crystals from ethanol, mp 193°C) (Found: C 79.8, H 9.2, N 5.3. Calc. for $C_{17}H_{23}NO$: C 79.3, H 9.0, N 5.4%). NMR spectra were consistent with the literature[27] and provided extra information. δ_H 7.60–7.56 (2H, m, *meta* H), 7.37–7.32 (1H, m, *para* H), 7.31–7.26 (2H, m, *ortho* H), 5.80 (br s, NH), 5.27 (m, $W_{h/2}$ 10, H2), 2.15 (dddd, *J* 12.2, 11.8, 5.0, 2.3, H4), 2.01–1.90 (2H, m, 1 × H6 and 1 × H3), 1.85 (dm, 1 × H3), 1.80–1.69 (2H, m, $H5_{eq}$ and 1 × H6), 1.53 (3H, br s, H7), 1.33 and 1.30 (2 × 3H, s, H9 and H10), 1.20 (dddd, *J* 12, 12, 12, 5.6, $H5_{ax}$). δ_C see Table 1. ν_{max} (Nujol)/cm^{-1} 3300, 1630, 1599, 1576, 1539, 1316, 1183, 1163, 1076, 1027, 929, 874, 803, 774, 720, 693, 668. *m/z* (GCMS) 258 (M + 1, 1%), 257 (M, 4), 163 (15), 162 (26), 136 (24), 122 (23), 121 (26), 106 (8), 105 (100), 93 (17), 79 (11), 77 (52).

Benzamine ***5d***

In a variation of the literature synthesis describing the hydrochloride salt of amine **5d**,[28] anhydrous sodium sulfate (1.00 g) was added to a solution of benzaldehyde (350 mg) in dry benzene (3 mL). Amine **1** (460 mg) in dry benzene (3 mL) was added. After 3 days the mixture was decanted from the sodium sulfate and filtered through a cotton wool plug. The residue was washed with further dry benzene. The combined filtrates, after evaporation of solvent, provided an oily residue that was dissolved in dry methanol (10 mL) and cooled (0°C) while sodium borohydride (0.52 g) was added. The reaction mixture was allowed to warm to room temperature overnight. The methanol was removed, aqueous ammonia (25%, 40 mL) was added, and the solution was extracted into diethyl ether (5 × 30 mL). These extracts were washed with brine, dried over sodium sulfate, and the solvent was removed to give the title compound, *(*R*)*-N-*benzyl-1-methyl-1-(4-methylcyclohex-3-en-1-yl)ethylamine [(*R*)-N-benzyl-8-amino-*p-*menth-1-ene]* **5d**, (0.71 g, 97%) as a viscous oil which was pure by GC analysis. δ_H 7.36–7.26 (5H, m, *ortho*- and *meta*-H and NH), 7.20 (1H, m, *para*-H), 5.40 (m, $W_{h/2}$ 11, H2), 3.68 (2H, AB system, J_{AB} 14, Δ_{AB} 12.7, benzylic H), 2.08–1.91 (3H, m, 1 × H6 and 2 × H3), 1.86 (m, 1 × H6), 1.80 (m, $H5_{eq}$), 1.64 (3H, br s, H7), 1.64 (obscured dddd, $J \approx 12$, ≈12, 4.9, 2.5, H4), 1.25 (dddd, *J* 12.5, 12.2, 11.4, 5.9, $H5_{ax}$), 1.08 and 1.07 (2 × 3H, s, H9 and H10). δ_C see Table 1. ν_{max} (neat)/cm^{-1} 3354, 3061, 3026,

Table 1. ^{13}C chemical shifts for the *p*-menthanes ($CDCl_3$ solution)

Compound	C1	C2	C3	C4	C5	C6	C7	C8	C9, C10	Other chemical shifts
5a	133.9	120.4	31.0	40.9	24.0	26.5	23.2	56.2	23.8, 24.1	169.3 (C11), 24.5 (C12)
5b	133.9	120.6	31.2	41.5	24.15	26.6	23.3	54.9	24.13, 24.3	154.5 (C11), 78.5 (C12), 28.4 (C13, C14, C15)
5c	134.0	120.4	31.0	41.3	24.18	26.6	23.2	56.7	24.13, 24.18	166.8 (C11), 136.1 (C12), 131.0 (C15), 128.5 (C13, C17), 126.6 (C14, C16)
5d	134.0	121.1	31.4	41.5	24.1	26.7	23.3	54.6	24.3, 24.4	141.7 (C12), 128.2/128.3 (C13, C14, C16, C17), 126.7 (C15), 46.2, (C11)
7	71.0	61.1	33.0	38.1	23.6	36.5	35.2	54.5	24.5, 24.9	154.2 (C11), 78.8 (C12), 28.4 (C13, C14, C15)
15	57.4	58.8	25.5	42.8	19.9	30.6	22.7	53.9	25.0, 25.8	
17	134.4	125.4	27.1	39.0	32.8	68.7	20.8	50.8	27.7, 28.6	
18	131.1	127.8	27.0	35.7	30.2	70.9	20.5	54.4	24.2, 24.7	171.0 (C11), 154.4 (C13), 78.7 (C14), 28.5 (C15, C16, C17), 21.2 (C12)
29	149.4	34.7	28.7	43.7	28.7	34.7	106.7	56.6	24.3, 24.3	169.5 (C11), 24.4 (C12)
33	134.6	127.5	27.3	40.1	23.7	26.8	38.8	56.1	24.0, 24.2	169.4 (C11), 24.5 (C12)
34[A]	133.5	121.9	31.8	42.3	24.31	27.1	23.6	54.0	24.30, 24.5	35.9 (C11), 16.6 (C12)

[A] In $[D_6]$benzene.

2962, 2924, 1644, 1581, 1538, 1493, 1451, 1381, 1308, 1160, 1070, 1026, 914, 799, 752, 696. *m/z* (GCMS) 243 (M, 1%), 228 (2), 160 (2), 149 (12), 148 (100), 146 (6), 136 (2), 121 (3), 106 (2), 93 (3), 92 (8), 91 (86).

Dibromide 7

Compound **5b** (770 mg) and *N*-bromosuccinimide (590 mg) were stirred (19 h) in acetone (40 mL). Flash chromatography of the product (6% diethyl ether, 94% hexane) gave starting material **5b** (R_F 0.16), followed by tert-*butyl 1-[(1*R*,3*S*,4*S*)-3,4-dibromo-4-methylcyclohexyl]-1-methylethylcarbamate [*N*-*BOC*-(1*S*,2*S*,4*R*)-8-amino-1,2-dibromo*-p-*menthane]* **7**, a highly viscous oil (R_F 0.10) (14% yield) (Found: C 43.9, H 6.7, N 3.2. $C_{15}H_{27}Br_2NO_2$ requires C 43.6, H 6.6, N 3.4%; found *m/z* 416.0440, 414.0459, 412.0473. $C_{15}H_{28}{}^{81}Br_2N$ (M + 1) requires 416.0440, $C_{15}H_{28}{}^{79}Br^{81}BrN$ (M + 1) requires 414.0461, $C_{15}H_{28}{}^{79}Br_2N$ (M + 1) requires 412.0481). δ_H 4.71 (dd, *J* 4.4, 2.9, H2), 4.35 (br s, $W_{h/2}$ 12, NH), 2.52 (dddd, *J* 12.3, 12.2, 4.7, 2.9, H4), 2.38 (ddd, *J*.13.5, 12.3, 2.9, $H3_{ax}$), 2.02 (1H, m, 1 × H6), 2.00 (m, $H3_{eq}$), 1.96 (3H, s, H7), 1.95 (1H, m, 1 × H6), 1.70–1.61 (2H, m, 2 × H5), 1.41 (9H, s, *t*-butyl group), 1.28 and 1.19 (2 × 3H, s, H9 and H10). δ_C see Table 1. ν_{max} (neat)/cm^{-1} 3445, 3358, 3281, 2974, 1731, 1694, 1667, 1504; with many strong peaks in the fingerprint region. *m/z* 416 (M + 1, 2%), 414 (M + 1, 4), 412 (M + 1, 2), 359 (10), 358 (3), 357 (20), 355 (9), 278 (5), 276 (4), 196 (9), 159 (3), 158 (38), 135 (7), 102 (36), 58 (100), 57 (21). The compound decomposed under GC conditions.

*Compound **9***

Benzamide **5c** (0.99 g, 3.85 mmol) and *N*-bromosuccinimide (0.71 g, 4.00 mmol) in acetone (50 mL) were stirred (4 h) until no starting amide remained (by TLC). The solvent was removed to give an oily residue that was triturated with hexane/diethyl ether (95 : 5; 5 × 10 mL). The combined extract was filtered and the solvent removed to give a viscous oil (0.6 g), which was subjected to flash chromatography on silica (hexane/diethyl ether; 95 : 5). Fractions containing the solid **9** were combined to give *(1*R*,6*R*,9*R*)-9-bromo-5,5,9-trimethyl-3-phenyl-2-oxa-4-azabicyclo[4.3.1]dec-3-ene* **9** (0.42 g, 32%) as colourless prisms, mp 112°C (from methanol), $[\alpha]_D$ –54° ($CHCl_3$) (Found: C 60.8, H 6.7, N 4.0. $C_{17}H_{22}BrNO$ requires C 60.7, H 6.6, N 4.2%). $\varepsilon_{245\,nm}$ (L mol^{-1}) 10628. δ_H 7.97–7.91 (2H, m, *ortho* H), 7.26–7.17 (3H, m, *meta*- and *para*-H), 4.62 (m, $W_{h/2}$ 7, H1), 2.70 (ddd, *J* 15.2, 5.1, 3.2, $H10_\alpha$), 2.46 (ddd, *J* 15.2, 5.0, 2.2, $H10_\beta$), 2.11 (dm, *J* 14.3, 5.9, 3.8, 2.5, $H7_\beta$), 2.01 (obscured m, $H7_\alpha$), 2.00 (obscured m, H6), 1.89 (obscured ddd, *J* 15.4, 12.2, ?, $H8_\alpha$), 1.86 (3H, s, H19), 1.82 (obscured dm, $H8_\beta$), 1.45 and 1.27 (2 × 3H, s, H17 and H18). δ_C 147.1 (C3), 136.3 (C11), 129.7 (C14), 128.3 (C12, C16), 127.9 (C13, C15), 81.6 (C1), 70.6 (C9), 59.5 (C5), 39.6 (C6), 35.3 (C8), 32.6 (C19), 30.4 and 30.9 (C17 and C18), 27.6 (C10), 23.8 (C7). ν_{max} (Nujol)/cm^{-1} 1720, 1667, 1447, 1381, 1360, 1331, 1243, 1191, 1157, 1106, 1093, 1057, 1027, 987, 804, 766, 745, 711, 694. *m/z* (GCMS) 337 (3%), 336 (M − Me from $C_{17}H_{22}{}^{81}BrNO$, 7), 335 (3), 334 (M − Me from $C_{17}H_{22}{}^{79}BrNO$, 7), 281 (2), 279 (2), 257 (4), 256 (30), 163 (7), 162 (50), 106 (8), 105 (100), 95 (29), 79 (12), 77 (39).

*Epoxide **15***

Amine **1** (490 mg, 3.2 mmol) and *N*-bromosuccinimide (730 mg, 4.1 mmol) were stirred (0°C) in tetrahydrofuran (40 mL) containing aqueous $HClO_4$ (0.5 M, 15 mL). After 1 h, sodium hydroxide solution (5 M, 10 mL) was added. After a further 1 h (0°C), water (40 mL) was added and the solution extracted into diethyl ether. The ether was washed with brine, dried over sodium sulfate, and the solvent was removed. The residue was chromatographed over silica (methanol/dichloromethane; 20 : 80) to provided *1-methyl-1-[(1*R*,3*R*,6*S*)-6-methyl-7-oxabicyclo[4.1.0]hept-3-yl]ethylamine [(1*S*,2*R*,4*R*)-8-amino*-p-*menthane-1,2-epoxide]* **15** as an oil (360 mg, 67%), >99% pure by GLC and NMR inspection (Found: *m/z* 169.1465. $C_{10}H_{19}NO$ requires 169.1467). δ_H 2.97 (d, *J* 5.3 Hz, H2), 2.05–1.98 (2H, m), 1.69–1.58 (2H, m), 1.50–1.44 (1H, dm), 1.40–1.30 (1H, m), 1.29 (3H, s, H7), 1.25–1.15 (1H, obscured m), 1.18 and 1.16 (2 × 3H, s, H9 and H10). δ_C see Table 1. ν_{max} (neat)/cm^{-1} 3354, 2959, 1654, 1596, 1458, 1431, 1381, 1312, 1257, 1211, 1176, 1096, 1023, 974, 915, 848, 826, 779, 747, 667. *m/z* (GCMS) 170 (M + 1, 1%), 169 (10), 155 (3), 154 (32), 136 (6), 126 (5), 110 (11), 97 (8), 96 (100), 95 (9), 94 (23), 84 (9), 82 (10), 71 (12).

*Aminomercuration of Amine **1** with Mercuric Acetate*

Amine **1** (500 mg, 3.26 mmol) in dichloromethane (20 mL) was stirred (8 days) with mercuric acetate (1.04 g, 3.26 mmol). The mixture was then added slowly to a stirred solution of sodium borohydride (250 mg, 6.52 mmol) in 5 M aqueous sodium hydroxide (2 mL) in an ice-salt bath. After 1 h, saturated sodium chloride solution (20 mL) and diethyl ether (50 mL) were added, and the mixture was transferred to a separatory funnel. The contents were shaken and the organic (upper) layer collected. The aqueous layer was further extracted with diethyl ether when the organic layers were combined and dried (sodium carbonate). GCMS analysis showed aziridine **3** (39%), starting amine **1** (35%), and acetate **16** (26%). The mixture was chromatographed on silica (dichloromethane/methanol, 95 : 4; containing 1% aqueous ammonia). The products in order of increasing polarity were compounds **3** (30%), **16** (26%), and **1** (35%), although compounds **3** and **16** co-eluted in many fractions. These three products were all identified by comparison (GC, NMR) with authentic[1] compounds.

*Alcohol **17***

Amine **1** (380 mg, 2.48 mmol) in dry dichloromethane (30 mL), was dried over molecular sieves (3 and 5 Å, approximately 0.5 g). The dried solution was decanted from the sieves into an oven-dried flask and mercuric trifluoroacetate (1.05 g, 2.48 mmol) was added. The flask was sealed and the contents were stirred at room temperature (6 days) until comparison (GCMS) of a demercurated aliquot with earlier samples showed that the reaction had reached equilibrium. Volatile compounds present in the organic extract were starting amine **1**, aziridine **3**, and a new compound **17** (4 : 12 : 81 by GCMS). The reaction mixture was cooled in an ice bath and a prechilled solution of sodium borohydride (310 mg, 8.19 mmol) in 2 M NaOH (20 mL) was added. When the resultant solution had settled (1 h, 0°C) it was twice filtered through filter paper, which was washed with dichloromethane. The organic layers provided crude crystalline material (220 mg) which contained an oily impurity. Trituration with small quantities of diethyl ether removed the oily impurity and left crystals (80 mg, 19%) of *(1*RS*,5*SR*)-5-(1-amino-1-methylethyl)-2-methylcyclohex-2-en-1-ol [(4*RS*,6*SR*)*-8-amino-6-hydroxy-p-*menth-1-ene]* **17**, as colourless prisms, mp 108–109°C (from diethyl ether) (Found: *m/z* 154.1229, 152.1195. $C_9H_{16}N_1O_1$ requires 154.1232 (M − CH_3, molecular ion was not observed), $C_{10}H_{16}O_1$ requires 152.1201 (M − NH_3)). X-ray analysis showed the presence of one water of crystallization per product molecule. δ_H 5.55 (m, $W_{h/2}$ 9, H2), 4.00 (dd, *J* 3.5, 2.3, H6), 2.09 (dm, *J* 16.7, ?, $H3_{eq}$), 1.95 (ddd, *J* 13.5, 4.1, 2.3, $H5_{eq}$), 1.76 (3H, br s, H7), 1.71 (obscured dm, *J* 16.7, ?, $H3_{ax}$), 1.57 (dddd, *J* 13.5, 11.2, 4.1, 2.3, H4), 1.49 (3H, br s, NH_2 and OH), 1.35 (ddd, *J* 13.5, 13.5, 3.5, $H5_{ax}$), 1.06 and 1.04 (2 × 3H, s, H9 and H10). δ_C see Table 1. ν_{max} (Nujol)/cm^{-1} 3447, 3341, 3321, 3269, 3185, 2720, 1613, 1170, 1052, 1033, 964, 806. *m/z* (GCMS) 154 (M − CH_3, 6%), 153 (3), 152 (M − NH_3, 11%), 151 (M − H_2O, 5%), 138 (2), 137 (23), 136 (34), 134 (19), 119 (30), 110 (12), 109 (100), 107 (12), 96 (11), 95 (48), 94 (23), 93 (29), 92 (11), 91 (50), 84 (11), 83 (11), 82 (12), 79 (40), 77 (53), 70 (67).

*Acetate **18***

Compound **5b** (600 mg, 2.37 mmol) and mercuric acetate (760 mg, 2.38 mmol) were stirred in a solution of dichloromethane (40 mL). Periodically an aliquot was worked up by addition to excess sodium borohydride in aqueous sodium hydroxide solution at 0°C, extraction into diethyl ether, and analysis by GC. After 7 days no further reaction was observed and the solution was cooled (ice-salt bath) and added carefully to a stirred solution of sodium borohydride (190 mg, 5 mmol) in aqueous sodium hydroxide (1 M, 20 mL) held at −5°C.

After 4 h at −5°C, the mixture (excluding the precipitated metallic mercury) was transferred to a separatory funnel and extracted into diethyl ether. Analysis of the extract showed starting material **5b** and a new compound **18** (58 : 42 by GC). Chromatography over silica gel gave first starting material (330 mg, 55%, eluted with hexane), followed by *(1*RS*,5*SR*)-5-{1-[(*tert-*butoxycarbonyl)amino]-1-methylethyl}-2-methylcyclohex-2-en-1-yl acetate [(4*RS*,6*SR*)-*N*-BOC-8-amino-*p*-menth-1(2)-en-6-yl acetate]* **18** (270 mg, 37%, in hexane/diethyl ether 70 : 30) as colourless prisms, mp 132°C (from hexane/diethyl ether) (Found: C 65.9, H 9.7, N 4.6. $C_{17}H_{29}NO_4$ requires C 65.6, H 9.4, N 4.5%). δ_H 5.67 (ddd, *J* 7.2, 3.6, 1.8, H2), 5.21 (m, $W_{h/2}$ 8, $H6_{eq}$), 4.33 (br s, $W_{h/2}$ 10, NH), 2.34 (dddd, *J* 13.7, 11.3, 4.1, 2.0, H4), 2.08 (dm, *J* 17.4, ?, $H3_{eq}$), 2.02 (3H, s, acetate Me), 1.93 (ddd, *J* 14.0, 4.1, 2.1, $H5_{eq}$), 1.75 (dm, *J* 17.6, ?, $H3_{ax}$), 1.65 (3H, m, $W_{h/2}$ 7, H7), 1.40 (9H, s, *t*-butyl Me), 1.41–1.32 (obscured m, $H5_{ax}$), 1.23 and 1.16 (2 × 3H, s, H9 and H10). δ_C see Table 1. ν_{max} (Nujol)/cm^{-1} 3380, 1720, 1716, 1511, 1365, 1289, 1251, 1178, 1159, 1067, 1047, 1029, 1009, 912. *m*/*z* (GCMS) 196 (M − 115, molecular ion not observed, 1%), 195 (2), 158 (22), 135 (10), 134 (8), 119 (15), 103 (6), 102 (100), 94 (10), 93 (16), 91 (11), 79 (12), 77 (8).

*Acetate **19***

Amine **5d** (0.88 g, 3.62 mmol) and mercuric acetate (1.16 g, 3.64 mmol) were stirred (24 h) in dichloromethane (20 mL). Workup by cooling and addition to a chilled solution of sodium borohydride (0.57 g, 15 mmol) in aqueous sodium hydroxide (1 M, 100 mL), as described above for compound **18**, followed by flash chromatography (hexane/diethyl ether, 95 : 5) provided *(1*R*,4*R*,5*R*)-6-benzyl-4,7,7-trimethyl-6-azabicyclo[3.2.1]oct-4-yl acetate [(1*R*,2*R*,4*R*)-N-benzyl-2,8-azacineole-1-acetate]* **19** as a colourless viscous oil (0.95 g, 87%) (Found: C 75.3, H 9.2, N 4.1. $C_{19}H_{27}NO_2$ requires C 75.7, H 9.0, N 4.6%). δ_H (CD_2Cl_2) 7.37–7.18 (five aromatic H), 3.96 and 3.66 (ABq, J_{AB} −13.4, two benzylic H), 3.57 (H2), 1.99 (H3β), 1.92 (acetate Me), 1.87 (H6α) 1.76 (H4), 1.67 (H6β), 1.66 (H5β), 1.65 (H3α), 1.58 (H5α), 1.19 and 1.05 (2 × 3H, s, H9 and H10), 0.95 (3H, H7); with $J_{2,3\alpha} \approx 0$, $J_{2,3\beta}$ 6.8, $J_{3\alpha,3\beta}$ −11.0, $J_{3\alpha,4} \approx 0$, $J_{3\beta,4}$ 4.7, $J_{3\beta,5\beta}$ 2.2, $J_{4,5\alpha}$ 3.0, $J_{4,5\beta}$ 2.2, $J_{5\alpha,5\beta}$ −13.6, $J_{5\alpha,6\alpha}$ 13.6, $J_{5\alpha,6\beta}$ 6.2, $J_{5\beta,6\alpha}$ 6.9, $J_{5\beta,6\beta}$ unavailable, and $J_{6\alpha,6\beta}$ −14.0. δ_C 170.6 (C11), 142.8 (C14), 129.9 (C15 and C19); 128.3 (C16 and C18), 126.9 (C17), 85.7 (C1), 67.9 (C2), 64.1 (C8), 55.3 (C13), 46.1 (C4), 32.9 (C6), 30.4 (C3), 25.7 and 24.2 (C9 and C10), 24.8 (C5), 22.5 (C12), 22.4 (C7). ν_{max} (neat)/cm^{-1} 3026, 2972, 2926, 1731, 1495, 1455, 1366, 1301, 1258, 1209, 1154, 1114, 1087, 1022, 932, 828, 734, 700, 610. *m*/*z* (GCMS) 302 (M + 1, 3%), 301 (M, 10), 286 (6), 258 (7), 242 (6), 241 (4), 227 (7), 226 (40), 187 (5), 186 (30), 184 (5), 92 (8), 91 (100).

*Alcohol **22***

Acetate **19** was reduced (24 h, room temp.) with lithium aluminium hydride in diethyl ether. Normal workup gave crude *(1*R*,4*R*,5*R*)-6-benzyl-4,7,7-trimethyl-6-azabicyclo[3.2.1]octan-4-ol [(1*R*,2*R*,4*R*)-N-benzyl-1-hydroxy-2,8-azacineole]* **22** (96% yield) which was sublimed under vacuum to give small colourless chunks, mp 90–91°C (Found: C 79.1, H 10.1, N 5.1. $C_{17}H_{25}NO$ requires C 78.7, H 9.7, N 5.4%). δ_H 7.32–7.16 (five aromatic H), 3.94 and 3.62 (ABq, J_{AB} −13.2, 2 × H11), 2.70 (H2), 1.96 (H3α), 1.93 (H3β), 1.90 (H6α), 1.73 (H4), 1.64 (H5β), 1.60 (H5α), 1.23 (H6β), 1.16 and 1.05 (2 × 3H, s, H9 and H10), 0.72 (3H, H7); with $J_{2,3\alpha} \approx 0$, $J_{2,3\beta}$ 5.0, $J_{3\alpha,3\beta}$ −11.5, $J_{3\alpha,4} \approx 0$, $J_{3\beta,4}$ 4.5, $J_{3\beta,5\beta}$ unavailable, $J_{4,5\alpha}$ 3.1, $J_{4,5\beta}$ 2.5, $J_{5\alpha,5\beta}$ −13.8, $J_{5\alpha,6\alpha}$ 13.8, $J_{5\alpha,6\beta}$ 5.7, $J_{5\beta,6\alpha}$ 7.9, $J_{5\beta,6\beta}$ small, and $J_{6\alpha,6\beta}$ −13.8. δ_C 142.3 (C12), 129.5 (C13 and C17), 127.9 (C14 and C16), 126.6 (C15), 73.9 (C1), 70.5 (C2), 63.4 (C8), 55.0 (C11), 45.9 (C4), 34.0 (C6), 29.9 (C3), 28.1 (C7), 25.6 and 24.7 (C9 and C10), 24.6 (C5). ν_{max} (Nujol)/cm^{-1} 3329, 1298, 1251, 1221, 1163, 1091, 1070, 1025, 973, 910, 750, 720, 697. *m*/*z* (GCMS) 260 (M + 1, 2%), 259 (M, 10), 245 (6), 244 (30), 226 (10), 187 (9), 186 (62), 184 (11), 110 (6), 92 (9), 91 (100), 83 (12).

*Compound **33***

β-Pinene **30** and NBS in anhydrous acetonitrile afforded crude allylic amide **33** by the literature method.[24] This material was used in a crude state for further reactions, as chromatography led to significant decomposition. Chromatography (ether/hexane) provided a small amount of pure sample with ^{1}H NMR, IR, and mass spectra identical with the literature.[24] δ_C see Table 1, where some assignments, confirmed by DEPT studies, are different from the literature.[24]

*Compound **29***

Crude bromide **33** was reduced with zinc powder in glacial acetic acid by following the literature method.[24] The product, a mixture of 8-acetamido-*p*-menth-1(7)-ene **29** and its endocyclic double-bond isomer (approximately 50 : 50) were chromatographed to afford compound **29** as colourless crystals (∼16% yield from compound **30**), mp 113–114°C (from hexane/ether; lit.[24] 123–125°C). All spectra, except ^{13}C NMR assignments, were identical to the literature.[24] δ_C: see Table 1.

The reagents which failed to convert amide **29** into amine **27** included sodium peroxide,[29] potassium hydroxide in refluxing dioxan/water,[30] refluxing methanol containing sodium acetate, and methyl lithium in refluxing ether/dioxan.[31]

*Amine **34***

β-Pinene (1.40 g, 10.1 mmol) and NBS (2.10 g, 11.8 mmol) were vigorously stirred (2 h) in acetonitrile (anhydrous, 40 mL). Sodium borohydride (1.15 g, 30.3 mmol) was added and the reaction mixture was stirred for an additional hour. Sodium hydroxide solution (2%, 30 mL) was added and after 1 h the pH was adjusted to 2 with hydrochloric acid, and the solution was then extracted with diethyl ether to remove neutrals. The aqueous layer was adjusted to pH 14 (2% NaOH solution) and the product extracted into diethyl ether. The resultant colourless oil (1.00 g) comprised compound **34** and the bicycle **35** (90 : 10 by GCMS). Trituration of the oil with small volumes of pentane (with the aid of an ultrasonic cleaning bath) removed all traces of the minor isomer and left N-*ethyl-1-methyl-1-(4-methylcyclohex-3-en-1-yl)ethylamine [*N*-ethyl-8-amino-*p*-menth-1-ene]* **34** (46% yield), >99% pure by GCMS and NMR. A distilled sample (bp 79°C/0.8 mmHg) appeared to have attracted carbon dioxide from the atmosphere and microanalysis showed approximately 0.2 mol equivalents of the bicarbonate salt (Found: C 75.6, H 12.3, N 7.4. $C_{12}H_{23}N$ requires C 79.5, H 12.8, N 7.7%. $C_{12}H_{23}N + 0.2(H_2CO_3)$ requires C 75.6, H 12.2, N 7.2%) (Found: *m*/*z* 182.1904, 181.1818. $C_{12}H_{24}N$ (M + 1) requires 182.1908, $C_{12}H_{23}N$ requires 181.1830). δ_H ([D_6]benzene) 5.45 (m, $W_{h/2}$ 11, H2), 2.44 (ddd, *J* 14.2, 7.1, 7.1, 1 × H11), 2.41 (ddd, *J* 14.2, 7.1, 7.1, 1 × H11), 1.81–2.00 (4H, m, 2 × H3 and 2 × H6), 1.78 (dm, width 28 Hz, $H5_{eq}$), 1.65 (3H, br s, H7), 1.46 (dddd, *J* 12.2, 11.1, 4.9, 2.5, H4), 1.16 (dddd, *J* 12.2, 12.2, 12.2, 5.5, $H5_{ax}$), 0.99 (3H, t, $J_{11,12}$ 7.1, H12), 0.93 and 0.92 (2 × 3H, s, H9 and H10). δ_C: see Table 1. ν_{max} (Nujol)/cm^{-1} 3315, 1249, 1221, 1183, 1164, 1107, 1021, 916. *m*/*z* (GCMS) 182 (M + 1, 0.1%), 181 (M, 0.3), 166 (1), 136 (1), 98 (5), 87 (6), 86 (100).

*Amine **35***

β-Pinene **30** (1.40 g, 10.1 mmol) and NBS (2.10 g, 11.8 mmol) were vigorously stirred (2 h) in acetonitrile (anhydrous, 40 mL) exactly as described above in the synthesis of compound **34**, except that now the reaction was quenched with excess sodium borohydride (191 mg, 5.05 mmol). The product, a colourless oil (0.95 g), was a mixture of compounds **32** and **31** (85 : 15 by GCMS). Careful trituration of the oil with small volumes of pentane (with the aid of an ultrasonic cleaning bath) extracted compound **35** from compound **34**. *6-Ethyl-7,7-dimethyl-4-methylene-6-azabicyclo[3.2.1]octane [*N*-ethyl-1,7-dehydro-2,8-azacineole]* **35**, a colourless volatile oil (41% yield), was distilled (bp 45°C/0.1 mmHg) to provide a sample >98% pure (by GC and NMR) (Found: *m*/*z* 164.1440. $C_{11}H_{18}N_1$ (M − CH_3) requires 164.1439). δ_H ([D_6]benzene; *p*-menthane skeletal numbering) 4.60 (2H, br s, H7), 3.52 (d, H2), 2.56 and 2.52 (2 × dq, 2 × H11), 2.39 (ddd, H6α), 2.18 (ddd, H3β), 2.08 (br dd, H6β), 1.68 (br dddd, H5β), 1.61 (dddd, H4), 1.36 (dddd, H5α), 1.27 (dd, H3α), 1.08 (3H, t, H12), 1.05 and 1.04 (2 × 3H, s, H9 and H10); with $J_{2,3\alpha} \approx 0$, $J_{2,3\beta}$ 5.9, $J_{3\alpha,3\beta}$ −11.1, $J_{3\alpha,4}$ 0.7, $J_{3\beta,4}$ 4.6, $J_{3\beta,5\beta}$ 2.7, $J_{4,5\alpha}$ 3.2, $J_{4,5\beta}$ 2.9, $J_{5\alpha,5\beta}$ −13.4, $J_{5\alpha,6\alpha}$ 12.3,

$J_{5\alpha,6\beta}$ 7.4, $J_{5\beta,6\alpha}$ 8.1, $J_{5\beta,6\beta} \approx 0$, $J_{6\alpha,6\beta}$ −15.4, $J_{2,11a} < 1$, $J_{2,11b} < 1$, $J_{11a,11b}$ −12.6, and $J_{11,12}$ 7.1. δ_C ([D$_6$]benzene) 152.4 (C1), 104.6 (C7), 65.5 (C2), 61.1 (C8), 45.4 (C4), 39.5 (C11), 36.9 (C6), 30.9 and 20.9 (C9 and C10), 28.8 (C3), 28.3 (C5), 16.8 (C12). ν_{max} (neat)/cm^{-1} 3064, 2962, 2099, 1776, 1645, 1454, 1381, 1262, 1185, 1116, 884. m/z (GCMS) 180 (M + 1, 1%), 179 (M, 7), 165 (13), 164 (100), 136 (18), 124 (6), 122 (7), 119 (8), 93 (8), 91 (11), 79 (10), 77 (10).

Crystallography

Compound **9** (Fig. 1): $C_{17}H_{22}BrNO$, M 336.27, orthorhombic, space group $P2_12_12_1$ (no. 19), a 10.106(2), b 10.228(2), c 15.384(3) Å, V 1590.2(5) Å^3, F(000) 696, D_c 1.405 g cm^{-3}, μ 25.81 cm^{-1}, 2136 unique data ($2\theta_{max}$ 50°), R 0.0380 (for 1488 reflections with $I > 2\sigma(I)$), wR_2 0.1154 (all data).

Compound **17** (Fig. 2): $C_{17}H_{29}NO_4$, M 311.41, monoclinic, space group $P2_1$ (no. 4), a 10.010(3), b 9.3244(6), c 10.395(4) Å, β 110.40(2)°, V 909.4(4) Å^3, F(000) 340, $D_c(Z = 2)$ 1.137 g cm^{-3}, μ 0.80 cm^{-1}, 1910 unique data ($2\theta_{max}$ 50°), R 0.0373 (for 1318 reflections with $I > 2\sigma(I)$), wR_2 0.1089 (all data).

Compound **18** (Fig. 4): $C_{10}H_{21}NO_2$, M 187.28, monoclinic, space group $P2_1/c$ (no. 14), a 6.116(2), b 20.585(4), c 8.796(4) Å, β 94.99(2)°, V 1103.2(7) Å^3, F(000) 416, $D_c(Z = 4)$ 1.128 g cm^{-3}, μ 0.77 cm^{-1}, 1943 unique data ($2\theta_{max}$ 50°), R 0.0673 (for 1038 reflections with $I > 2\sigma(I)$), wR_2 0.1820 (all data).

Intensity data at 296 K were collected on an Enraf–Nonius CAD4 four-circle diffractometer using graphite monochromated $Mo_{K\alpha}$ radiation (λ 0.71073 Å) in the ω–2θ scan mode. Lattice dimensions were determined by a least-squares fit of the setting parameters of 25 independent reflections. Data reduction and empirical absorption corrections (ψ-scans) were performed with the *WINGX* package.[32] Structures were solved by direct methods with *SHELXS* and refined by full-matrix least-squares analysis with *SHELXL97*.[33] All non-hydrogen atoms were refined with anisotropic thermal parameters, and hydrogen atoms were constrained at estimated positions using a riding model. Water hydrogen atoms were first located from difference maps then restrained in these positions. The atomic nomenclature is defined in Figs 1, 2, and 4 drawn with *ORTEP3*.[34] The unit cell diagram (Fig. 3) was produced with the program *PLUTON*.[35] Crystallographic data in CIF format are available from the Cambridge Crystallographic Data Base (depositions: 205668, compound **9**; 205669, compound **17**; and 205670, compound **18**).

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