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UNUSUAL BASE-INDUCED REARRANGEMENT OF *EXO*-9-OXABICYCLO[4.2.1]NON-7-ENE OXIDE TO *EXO*-8-HYDROXYBICYCLO[3.3.0]OCTAN-2-ONE

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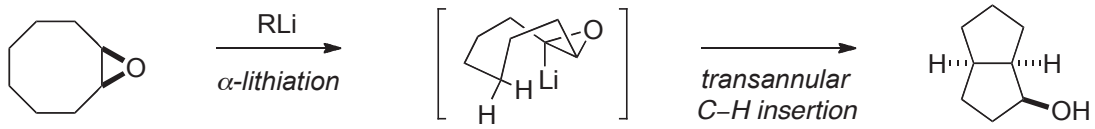
This paper is dedicated to Professor Albert Padwa on the occasion of his 75th birthday.

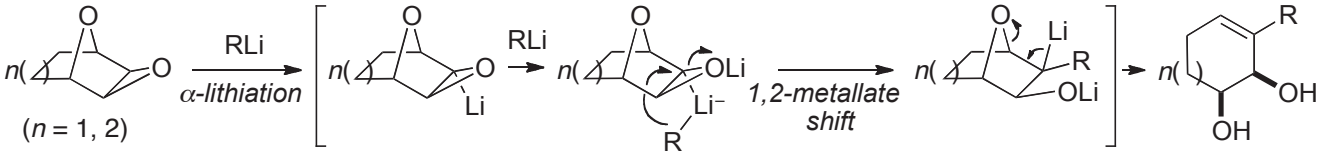
Abstract – Reaction of *exo*-9-oxabicyclo[4.2.1]non-7-ene oxide with *n*-BuLi gives *exo*-8-hydroxybicyclo[3.3.0]octan-2-one. Potential reaction pathways for this unusual rearrangement were evaluated with the aid of computational studies. The process is proposed to proceed by elimination to a transient allene oxide, which rearranges to a *trans*-epoxide enolate before undergoing epoxide α-lithiation and transannular C–H insertion.

INTRODUCTION

Epoxides are versatile synthetic intermediates.[4] Their reactions are dominated by the electrophilic nature of the epoxide, generally involve cleavage of the strained three-membered ring, and include a wide range of nucleophilic ring-openings and acid- and base-induced isomerisation reactions. Building on studies by Cope,[5] Crandall[6] and Mioskowski[7] on the carbenoid nature of α-lithiated epoxides,[8] we have reported on the (enantioselective) organolithium-induced transannular desymmetrisation of cyclooctene oxides (eg, Scheme 1),[9] and alkylative double ring-opening of epoxides of dihydrofurans, dihydropyrans, and of oxabicyclo[*n*.2.1]alkenes (*n* = 1, 2) (Scheme 2).[10] Examination of this chemistry for the latter substrate class when *n* = 3 has led to an unusual rearrangement, which constitutes the topic of the present paper.



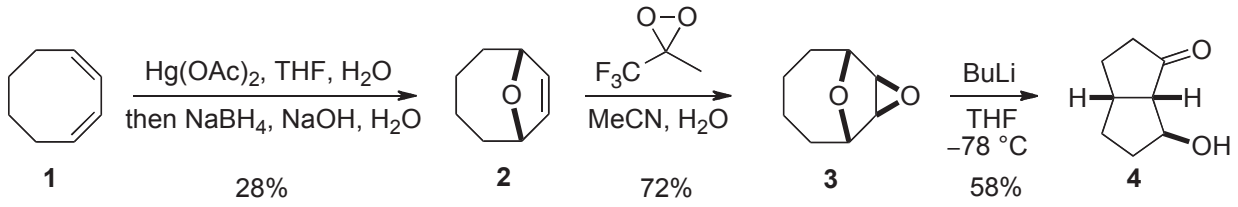
Scheme 1. α-Lithiation – transannular C–H insertion of *cis*-cyclooctene oxide



Scheme 2. Alkylative double ring-opening of epoxides of oxabicyclo[*n*.2.1]alkenes (*n* = 1, 2)

RESULTS AND DISCUSSION

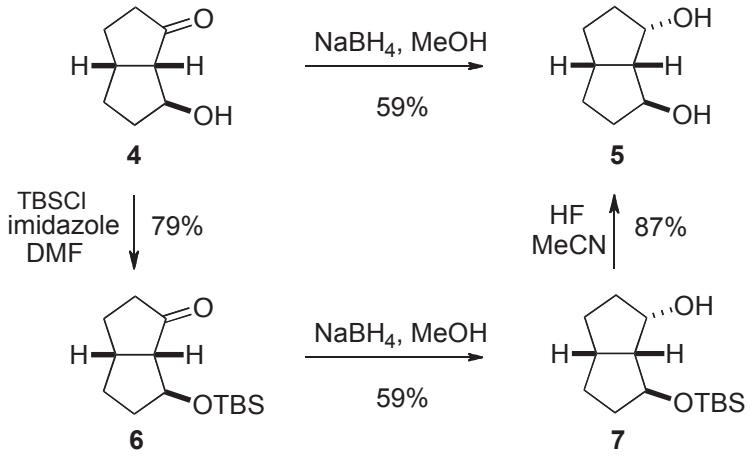
The synthesis of *exo*-9-oxabicyclo[4.2.1]non-7-ene oxide (**3**) (Scheme 3) commenced with the preparation of the precursor 9-oxabicyclo[4.2.1]non-7-ene (**2**) by oxymercuration – demercuration of 1,3-cyclooctadiene (**1**) (28% yield, lit.[11] 37% yield). Epoxidation of **2** with *in situ* generated methyl(trifluoromethyl)dioxirane[12] gave a single isomer (by crude ^{1}H NMR analysis), the epoxide **3** being obtained in 72% yield. By analogy with epoxidations of oxabicyclo[*n*.2.1]alkenes (*n* = 1, 2) and homotropenes (**2**, where O is replaced by N-R),[13] the epoxidation of **2** is expected to occur on the less-hindered *exo*-face. As *exo*-7,8-epoxy-*N*-(benzyloxycarbonyl)-9-azabicyclo[4.2.1]nonane (**3**, where bridge O is replaced by N-Z) exhibits no significant ^3J coupling between epoxide and bridgehead H's (dihedral angle close to 0°), whereas 3.6 Hz is observed for the corresponding *endo*-epoxide (dihedral angle close to 90°),[13a] then the absence of any such coupling for **3** provides further support for the *exo*-configurational assignment.



Scheme 3. Synthesis and rearrangement of epoxide **3**

Application of the standard alkylative double ring-opening reaction conditions used in Scheme 2 [*n*-BuLi (2.5 equiv.), THF, –78 °C to 25 °C, 16 h] to epoxide **3** gave *exo*-8-hydroxybicyclo[3.3.0]octan-2-one (**4**)[14] (58% yield, Scheme 3), rather than the corresponding cyclooctenediol which would have been expected if chemistry analogous to that shown in Scheme 2 was followed. *Exo*-**4** could also be obtained enantioenriched (85:15 er, absolute configuration of dominant enantiomer not known), albeit in only 16%

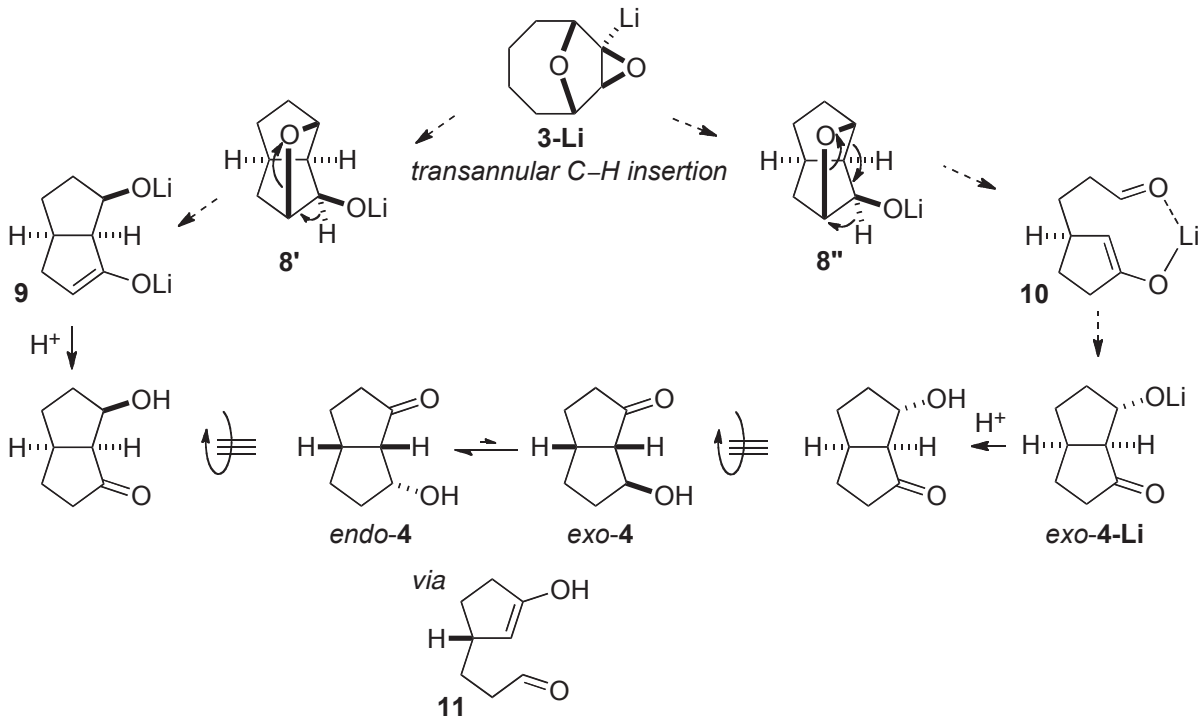
yield, from epoxide **3** by using *i*-PrLi (2.5 equiv.) in the presence of the external chiral ligand (–)-sparteine (2.5 equiv.) in ether (–78 ºC to 25 ºC, 16 h).[9,10,15] The structural and stereochemical assignment of **4** was unambiguously established through both spectral comparisons and chemical manipulation. Comparison of the ^{1}H and ^{13}C NMR data with that known for both *exo*- and *endo*-isomers was indicative for *exo*-**4**.[14c,16] Reduction of **4** ($NaBH_4$, MeOH, 0 ºC, 1 h) gave the non-*meso* diol **5**[17] (59% yield), consistent with **4** being the *exo*-isomer (Scheme 4). To exclude the possibility that hydroxyl-directed reduction of the *endo*-isomer had resulted in the non-*meso* diol **5** we further derivatised **4** as the TBS ether **6** (having different spectral characteristics to the known[18] *endo*-TBS ether); reduction to alcohol **7** and desilylation again gave the non-*meso* diol **5**.



Scheme 4. Transformations supporting the stereochemical assignment of **4**

The unusual rearrangement of epoxide **3** to *exo*-alcohol **4** merits some discussion. Initial epoxide α-lithiation might reasonably be considered to be the first step, in common with the chemistry shown in Schemes 1 and 2. The difference in reactivity seen between the current ether-bridged cyclooctene oxide **3** and the cycloheptene- and cyclohexene-oxide ether-bridged systems studied earlier (Scheme 2) could then relate to the propensity for such medium-ring systems to engage in transannular chemistry (eg, Scheme 1).[5,9,19] That is, a combination of steric impediment to the 1,2-metallate shift[20] due to the rear methylene groups, together with the closeness of one of the methylene CHs to the carbenoid centre in **3-Li** could retard the 1,2-metallate process and accelerate a transannular C–H insertion. This mechanistic scenario would lead to tricyclic alkoxide **8** (Scheme 5). Such tricyclic systems are known,[21] but attempted low temperature trapping of the putative tricyclic intermediate **8** [*n*-BuLi (1.1 equiv.), –78 ºC, 3 h] resulted only in recovery of starting epoxide **3**. In the present case, excess base could drive an elimination (shown in **8'**) with relief of ring strain to give *endo*-alkoxide enolate **9**. A difficulty then arises in satisfactorily progressing **9** to the observed *exo*-alcohol **4**, which would require a retro-aldol – aldol process in the work-up (pH 7 buffer). Even if such an interconversion occurred, *endo*-alcohol **4** is known

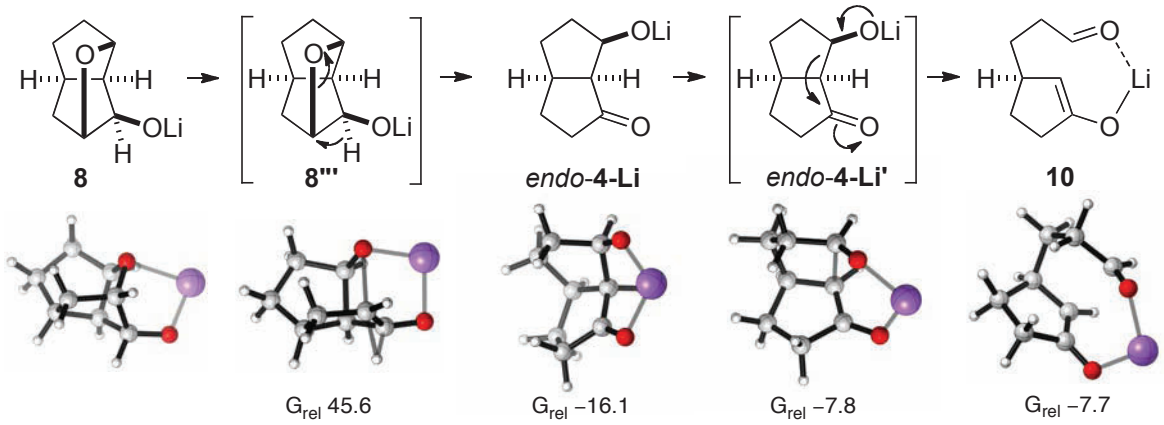
to predominate at equilibrium (62:11:27, *endo*-**4** : *exo*-**4** : bridged aldol epimers),[14c] so any reaction pathway proceeding though *endo*-alcohol **4** can be ruled out.



Scheme 5. Possible reaction pathways from **3-Li** to alcohol **4**

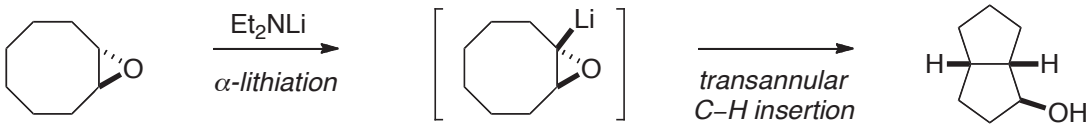
An alternative, more speculative suggestion for the generation of *exo*-alcohol **4** is by way of the concerted 1,2-H shift/retro-aldolate process[22] shown in tricyclic intermediate **8"** to directly generate an enolate aldehyde **10** (Scheme 5), which might undergo a kinetic aldol ring closure with opposite selectivity to that observed under acidic conditions.[23] DFT optimisations performed at the wB97XD/6-31G(d) level of theory in a CPCM solvation model of THF[24] were carried out to gauge the feasibility of these steps. The optimised structure of the intermediate tricyclic alkoxide **8** shows the alkoxide C–H to be antiperiplanar to the ethereal C–O bond, and is elongated by 0.02 Å relative to typical C–H distances indicative of σ_{CH}–σ^*_{CO} hyperconjugation (Scheme 6). In model calculations where the Li cation was replaced with a proton, it was possible to locate a TS for a concerted 1,2-H shift/retro-aldol, forming the enol aldehyde **11**, although the barrier is prohibitively high (75 kcal/mol). Attempts to locate a similar structure with Li (cf, **8"**) were unsuccessful since, on 1,2-hydride shift resulting in ether C–O cleavage, the Li cation moves to stabilise the developing alkoxide and so avoids a concomitant retro-aldolate process which would form the enolate aldehyde **10**; an unfeasibly high activation barrier of 46 kcal/mol was also calculated for this process.[25] The transition state for the 1,2-hydride shift (**8"'**) leads to the formation of the *endo* β-lithiooxyketone *endo*-**4-Li** (Scheme 6), downhill in free energy by 16 kcal/mol. The retro-aldolate TS

endo-**4-Li'** lies uphill by only 8.3 kcal/mol, and leads to a potential energy surface which is extremely flat, such that further elongation of the C–C bond causes a very slight decrease in energy. The energy minimum found for the enolate aldehyde **10** has a C---C separation of 2.5 Å and so resembles the TS geometry closely.[26] Even if enolate aldehyde **10** could be formed by some means, no TS exists (at this level of theory/solvation model)[24] for the formation of *exo*-**4-Li** (which is 3.5 kcal/mol higher in energy than *endo*-**4-Li**). Instead the potential energy falls continuously from enolate to product.



Scheme 6. Tricyclic alkoxide **8** to enolate aldehyde **10** by 1,2-H shift then retro-aldolate

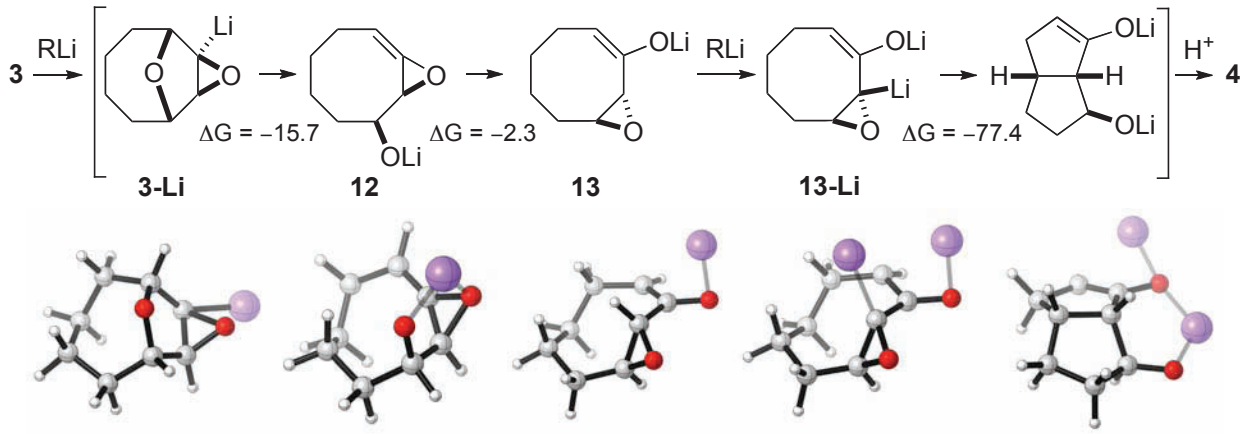
With no experimental or computational support for the formation of *exo*-**4** from epoxide **3** by either of the two pathways proceeding by way of initial epoxide α-lithiation – transannular C–H insertion and a retro-aldol(ate) process discussed above (Schemes 5 and 6), we considered a pathway passing through a lithiated *trans*-cyclooctene oxide. Cope and co-workers had originally shown that lithiated *trans*- and *cis*-cyclooctene oxides undergo stereospecific transanular insertion chemisty, with the *cis*-isomer proceeding as in Scheme 1 and, importantly in the current context, the *trans*-isomer leading to the *exo*-alcohol (Scheme 7).[5,27]



Scheme 7. α-Lithiation – transannular C–H insertion of *trans*-cyclooctene oxide[5,27]

A feasible pathway for the formation of *exo*-alcohol **4** from epoxide **3**, which proceeds through a *trans*-epoxide, is outlined in Scheme 8. **3-Li** is aligned for *anti*-elimination (Li–C–C–O dihedral angle is 169°) to give a transient allene oxide **12**.[28,29] Such a process is not seen for epoxides of

oxabicyclo[*n*.2.1]alkenes (*n* = 1, 2) (Scheme 2) due to the more favorable 1,2-metallate shift process and higher energy TSs to more strained allene oxides. In the present case, the ether bridge may also retard the transannular pathway (cf, Scheme 1) relative to the elimination. The allene oxide **12** can rearrange to the *trans*-epoxide enolate **13**. Regioselective lithiation of *trans*-epoxide enolate **13** to give **13-Li** followed by transannular C–H insertion finds precedent in the work of Cope discussed above (Scheme 7) and in the work of Crandall and Chang concerning α-lithiation – transannular C–H insertion of the mono epoxide of **1**.[30] While transition states could not be located, thermodynamics are favourable for the formation of each of the intermediates proposed.



Scheme 8. Allene oxide pathway from epoxide **3** to alcohol **4**

In summary, an unusual base-induced reaction of *exo*-9-oxabicyclo[4.2.1]nonene oxide (**3**) to *exo*-8-hydroxybicyclo[3.3.0]octan-2-one (**4**) has been discovered. A rationalisation, which has its origins in classic transannular chemistry studies by Cope over half a century ago, provides a satisfactory explanation as to why only the *exo*-isomer is observed.

EXPERIMENTAL

All reactions requiring anhydrous conditions were conducted in flame- or oven-dried apparatus under an atmosphere of argon. Syringes and needles for the transfer of reagents were dried at 140 ºC and allowed to cool in a desiccator over P_2O_5 before use. Ethers were distilled from sodium benzophenone ketyl under argon; CH_2Cl_2 from CaH_2 under argon. External reaction temperatures are reported unless stated otherwise. Reactions were monitored by TLC, using commercially available aluminium-backed plates, precoated with a 0.25 mm layer of silica containing a fluorescent indicator (Merck). Organic layers were dried over $MgSO_4$. Column chromatography was carried out on Kieselgel 60 (40–63 μm). Light petroleum refers to the fraction with bp 40–60 ºC. Melting points were determined using a Gallenkamp

hot stage apparatus and are uncorrected. Elemental analysis was performed by Elemental Microanalysis Limited, Okehampton, Devon, UK. IR spectra were recorded as thin films unless stated otherwise. Peak intensities are specified as strong (s), medium (m) or weak (w). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Brüker JEOL EX400 spectrometer. Chemical shifts are reported relative to $CHCl_3$ [δ H 7.26, δ C 77.0]. Coupling constants (*J*) are given in Hz. Chiral GC was performed at 100 ºC on a ThermoQuest CE Instruments TRACE GC, fitted with a CYDEX-β column.

9-Oxabicyclo[4.2.1]non-7-ene (2)

1,3-Cyclooctadiene (**1**) (6.2 mL, 50 mmol) and $Hg(OAc)_2$ (47.8. g, 150 mmol) in a mixture of THF (85 mL) and H_2O (85 mL) was stirred at 25 °C for 5 days. Aqueous NaOH (3 M, 65 mL) was added and stirring continued for a few min until the mixture became black. A solution of $NaBH_4$ (3.80 g, 100 mmol) in aqueous NaOH (3 M, 65 mL) was added over 30 min and mercury was observed to form. The mixture was saturated with NaCl and extracted with Et_2O (2 x 100 mL). The combined organic layers were washed with H_2O (2 x 100 mL), dried, filtered and concentrated under reduced pressure. Bulb-to-bulb distillation (50 °C / 5 mbar; lit.[11a] 74 °C / 10 mmHg) gave *alkene* **2** as a colourless oil (1.72 g, 28%); R_f 0.35 (50% Et_2O in petrol); ν_{max}/cm^{-1} 2920s br, 2855s, 1444m, 1090s and 1018s; ^{1}H NMR δ 5.80 (2H, s), 4.98 (2H, d, *J* 6.4), 1.92–1.85 (2H, m), 1.62–1.53 (4H, m) and 1.49–1.43 (2H, m); ^{13}C NMR δ 130.8, 80.0, 33.8 and 25.2.

***exo*-7,8-Epoxy-9-oxabicyclo[4.2.1]nonane (3)**

To a solution of *alkene* **2** (1.46 g, 11.8 mmol) and aqueous Na_2EDTA (400 μM, 60 mL, 24 μmol) in MeCN (90 mL) at 0 °C was added trifluoroacetone (11.6 mL, 130 mmol) from a pre-cooled syringe. The resulting homogeneous mixture was treated with a mixture of Oxone® (18.1 g, 58.8 mmol) and $NaHCO_3$ (7.90 g, 94.1 mmol) portionwise over 30 min, then stirred at 0 °C for 4.5 h. H_2O (450 mL) was added and the reaction mixture extracted with CH_2Cl_2 (3 x 450 mL). The combined organic layers were dried, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, 50% Et_2O in petrol) gave *epoxide* **3** as a white solid (1.18 g, 72%); R_f 0.25 (50% Et_2O in petrol); mp. 58 – 60 °C; (Found: C, 68.3; H, 8.7. $C_8H_{12}O_2$ requires C, 68.5; H, 8.6%); ν_{max}/cm^{-1} (KBr) 2928m, 2859m, 1456m, 1090s and 957s; ^{1}H NMR δ 4.32 (2H, d, *J* 6.9), 3.47 (2H, s), 1.98–1.83 (2H, m), 1.65–1.51 (4H, m) and 1.47–1.37 (2H, m); ^{13}C NMR δ 75.7, 58.4, 31.3 and 24.3; *m/z* [APCI +] 141 ($M + H^+$, 100%), 121 (30) and 105 (45).

***exo*-8-Hydroxybicyclo[3.3.0]octan-2-one (4)**

To a solution of *epoxide* **3** (80 mg, 571 μmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.2 M in

hexanes, 0.65 mL, 1.4 mmol) dropwise. The mixture was stirred at –78 °C for 5 h and then allowed to warm to 25 °C over 16 h. Phosphate buffer (pH 7, 5 mL) was added and the mixture extracted with EtOAc (2 x 10 mL). The combined organic layers were dried, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, 75% Et_2O in petrol) gave *hydroxy ketone* **4**[14] as a colourless oil (46 mg, 58%); R_f 0.15 (75% Et_2O in petrol); ν_{max}/cm^{-1} 3414s br, 2951s, 2872m, 1732s, 1461m and 1224m; ^1H NMR δ 4.15 (1H, br s), 2.85–2.78 (1H, m), 2.39 (1H, d, *J* 9.0), 2.11–2.05 (2H, m), 2.00–1.91 (2H, m), 1.53–1.43 (3H, m) and 1.27–1.02 (1H, m); ^{13}C NMR δ 220.8, 76.6, 61.7, 39.2, 37.9, 35.2, 30.6 and 26.4; *m/z* [CI + (NH_3)] 158 (M + NH_4^+, 100%) (Found: M + NH_4^+, 158.1183. $C_8H_{16}NO_2$ requires 158.1181).

(+)-*exo*-8-Hydroxybicyclo[3.3.0]octan-2-one (4)

To a solution of (–)-sparteine (0.33 mL, 1.44 mmol) in Et_2O (5 mL) at –78 °C was added *i*-PrLi[31] (1.5 M in petrol, 0.95 mL, 1.43 mmol) dropwise. After stirring at –78 °C for 1 h a solution of *epoxide* **3** (80 mg, 571 μmol) in Et_2O (3 mL) was added dropwise. The mixture was stirred at –78 °C for 5 h and then allowed to warm to 25 °C over 16 h. Aqueous HCl (0.5 M, 5 mL) was added and the mixture extracted with EtOAc (2 x 10 mL). The combined organic layers were dried, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, 75% Et_2O in petrol) gave *hydroxyketone* **4** as a colourless oil (13 mg, 16%); $[\alpha]_D^{25}$ +56 (*c* 1.0, $CHCl_3$); Chiral GC: 85:15 er (t_R(mn) 79.3 min, t_R(mj) 83.2 min); other data as above.

***endo*,*exo*-Bicyclo[3.3.0]octane-2,8-diol (5)**

To a solution of *hydroxyketone* **4** (30 mg, 214 μmol) in MeOH (2.5 mL) at 0 °C was added $NaBH_4$ (8 mg, 210 μmol). The resulting mixture was stirred at 0 °C for 1 h, neutralised by addition of aqueous HCl (2 M, few drops) and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, EtOAc) gave *diol* **5**[16] as a colourless oil (18 mg, 59%); R_f 0.20 (EtOAc); ν_{max}/cm^{-1} 3351s, 2946s, 1455m, 1350m, 1110m and 1065m; ^1H NMR δ 4.32–4.25 (2H, m), 3.06 (2H, br s), 2.61–2.52 (1H, m), 2.25 (1H, dd, *J* 16.4 and 7.2), 2.01–1.89 (2H, m), 1.79–1.73 (1H, m), 1.64–1.47 (3H, m), 1.31–1.25 (1H, m) and 1.21–1.11 (1H, m); ^{13}C NMR δ 74.1, 73.9, 54.8, 40.9, 35.7, 32.9, 30.9 and 29.3; *m/z* [CI + (NH_3)] 160 (M + NH_4^+, 100%) 124 (30), 107 (20), 96 (20) and 80 (30) (Found: M + NH_4^+, 160.1336. $C_8H_{18}NO_2$ requires 160.1338).

***exo*-8-(*tert*-Butyldimethylsilyloxy)bicyclo[3.3.0]octan-2-one (6)**

A mixture of *alcohol* **4** (40 mg, 285 μmol), TBSCl (55 mg, 365 μmol) and imidazole (50 mg, 734 μmol) in DMF (0.5 mL) was stirred for 16 h and then partitioned between Et_2O (2 mL) and H_2O (2 mL). The

organic layer was separated and washed with H_2O (2 x 1 mL), dried, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, 10% Et_2O in petrol) gave *silyl ether* **6** as a colourless oil (57 mg, 79%); R_f 0.30 (10% Et_2O in petrol); ν_{max}/cm^{-1} 2955s, 2857m, 1738s, 1463w, 1257m and 1050m; ^1H NMR δ 4.31 (1H, br s), 3.00–2.91 (1H, m), 2.50 (1H, d, *J* 9.2), 2.30–2.03 (4H, m), 1.64–1.55 (3H, m), 1.42–1.33 (1H, m), 0.88 (9H, s), 0.08 (3H, s) and 0.07 (3H, s); ^{13}C NMR δ 220.5, 77.9, 62.7, 39.5, 38.4, 36.5, 31.4, 26.9, 26.2, 18.4 and –4.4; *m/z* [GCMS CI + (NH_3)] 272 (M + NH_4^+, 60%), 255 (M + H^+, 65) and 197 (100) (Found: M + H^+, 255.1788. $C_{14}H_{27}O_2Si$ requires 255.1780).

***exo*,*endo*-8-(*tert*-Butyldimethylsilyloxy)bicyclo[3.3.0]octan-2-ol (7)**

To a solution of *ketone* **6** (52 mg, 204 μmol) in MeOH (2 mL) at 0 °C was added $NaBH_4$ (12 mg, 317 μmol). The resulting mixture was stirred at 0 °C for 1 h, neutralised by addition of aqueous HCl (2 M, few drops) and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, 10% Et_2O in petrol) gave *alcohol* **7** as a colourless oil (31 mg, 59%); R_f 0.20 (10% Et_2O in petrol); ν_{max}/cm^{-1} 3436m br, 2952s, 2858s, 1471m, 1463m and 1253m; ^1H NMR δ 4.33–4.29 (2H, m), 2.57–2.51 (1H, m), 2.32–2.26 (1H, m), 2.01–1.92 (1H, m), 1.85–1.49 (5H, m), 1.32–1.26 (1H, m), 1.23–1.14 (1H, m), 0.88 (9H, s), 0.08 (3H, s) and 0.07 (3H, s); ^{13}C NMR δ 74.3, 74.2, 56.0, 40.8, 36.7, 34.4, 31.0, 29.2, 25.8, 17.9, –4.3 and –4.8; *m/z* [GCMS CI + (NH_3)] 257 (M + H^+, 100%) (Found: M + H^+, 257.1935. $C_{14}H_{29}O_2Si$ requires 257.1935).

***endo*,*exo*-Bicyclo[3.3.0]octane-2,8-diol (5)**

To a solution of *silyl ether* **7** (25 mg, 98 μmol) in MeCN (0.5 mL) was added aqueous HF (48%, 100 μL). After 1 h the mixture was neutralised with solid $NaHCO_3$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, EtOAc) gave *diol* **5** as a colourless oil (12 mg, 87%); data as above.

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