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A novel boron trifluoride etherate mediated deep-seated rearrangement of an α,β-epoxyketone

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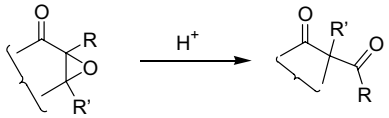
Abstract—Acid catalysed reaction of carvone epoxide **2** resulted in dimeric products **3** and **4**, in contrast to the expected ring contraction product. Reaction of β-methylcarvone epoxides **8** and **11** with acids furnished 2-acetyl-4-isopropenylcyclopentanones **9** and **14** containing a stereodefined quaternary carbon atom. On the other hand, the reaction of epoxides **8** and **11** with boron trifluoride etherate lacks the stereoselectivity and in addition, *anti*-epoxide **8** furnished lactone **18** via an unusual deep seated rearrangement.

1. Introduction

Epoxides are versatile intermediates in organic synthesis. The inherent polarity and strain of the three-membered ring makes epoxides susceptible to reactions with a large number of reagents. The synthetically useful reactions of epoxides include inter- and intramolecular nucleophilic ring opening, reduction to alcohols, deoxygenation to alkenes and more importantly, rearrangements to carbonyl compounds and allylic alcohols. Among the variety of functionalised epoxides, α,β-epoxy ketones have proven to be interesting and useful substrates in organic synthesis. The presence of a carbonyl group on the epoxide carbon provides the possibility for regio- and stereoselective transformations. In particular, acid catalysed rearrangement of appropriately substituted α,β-epoxy ketones to 1,3-dicarbonyl compounds has attracted the attention of various research groups (Eq. 1). When α,β-epoxy ketones are treated with Lewis acids, exclusive 1,2-carbonyl migration occurs in many cases if the carbonyl π-bond can achieve an orbital alignment that can result in delocalisation. When geometric constraints prevent the involvement of the carbonyl π-bond, participation of the Lewis acid catalyst can result in halohydrin formation. It is generally accepted that mono- and 1,1-disubstituted epoxides, give aldehydes on rearrangement with acids, but with 1,2-disubstituted, tri- and tetrasubstituted epoxides a variety of factors determine the outcome of the reaction. This includes the nature of the substituents on the epoxide, the stereochemistry at the epoxide oxygen, and the nature of the Lewis acid employed.[1,2] For the development of a convenient procedure for the enantioselective generation of 2-acetylcyclopentanones, we have investigated the acid catalysed rearrangement of the epoxides derived from carvone. These investigations revealed some unexpected rearrangements depending on the acid employed and the temperature of the reaction. Herein, we report the details of these investigations.



(1)

2. Results and discussion

It was expected that the Lewis acid mediated rearrangement of carvone epoxide **2** would generate optically active 2-acetyl-4-isopropenylcyclopentanone, a useful chiron in natural product synthesis. However, contrary to our expectation, reaction of carvone epoxide **2** with boron trifluoride etherate failed to generate the ring contracted product and furnished, exclusively, the dimeric compounds **3** and **4**, whose structures were deduced from their spectral data.[3] The reaction was found to be much more efficient with Amberlyst-15 in refluxing benzene and generated the dimers **3** and **4** in 77 and 20% yield, respectively. Formation of the dimers can be readily explained as depicted in Scheme 1. Acid

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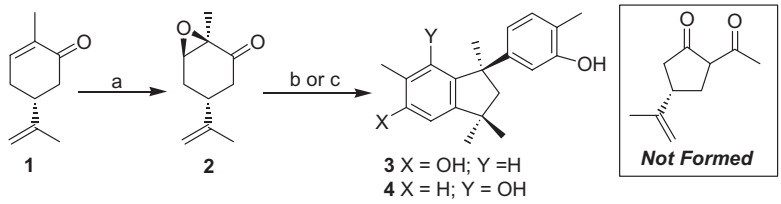
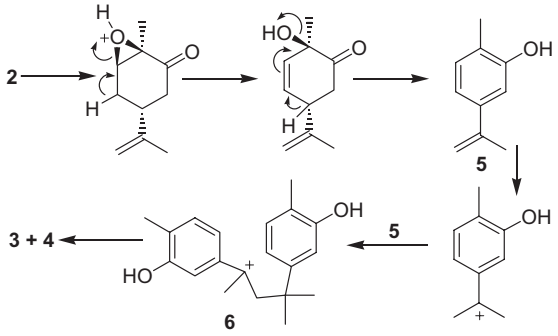


Scheme 1. Reagents and conditions: (a) 30% H_2O_2, 6 M NaOH, MeOH, 0 °C, 2 h, 70%; (b) $BF_3{\cdot}Et_2O$ (excess), 0.1 M CH_2Cl_2, rt, 10 min, **3**, 51% and **4**, 24%; (c) Amberlyst-15 (1:1 weight equivalent), 0.1 M C_6H_6, reflux, 2.5 h, **3**, 77% and **4**, 20%.

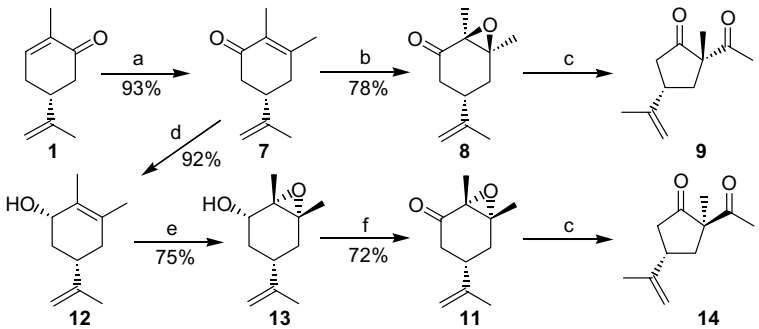
mediated rearrangement of epoxide **2** generates a tertiary allyl alcohol, which on dehydration generates styrene **5**. Dimerisation of the styrene **5** via cyclisation (at the *para*- or *ortho*-positions to the hydroxy group) of carbonium ion **6** generates the regioisomeric aryl indanols **3** and **4** (Scheme 2). As expected, dimers **3** and **4** were found to be racemic.



Scheme 2.

It was reasoned that the presence of a substituent at the β-position of carvone **1** would alter the course of the reaction, as the intermediate tertiary carbonium ion would be more favoured, and in addition also lead to acetylcyclopentanes containing a stereodefined quaternary carbon atom. Reaction of β-methylcarvone[4] **7** with 30% hydrogen peroxide and sodium hydroxide in methanol furnished the *anti*-epoxide **8** (Scheme 3).[5] As anticipated, reaction of *anti*-epoxide **8** with an excess of *p*-toluenesulfonic acid (*p*-TSA) in methylene chloride at room temperature for 4.5 h furnished β-diketone **9** in 74% yield in a highly stereoselective manner, whose structure was established from its spectral data. The reaction was found to be very slow with sub-stoichiometric amounts of *p*-TSA. The reaction was also found to proceed smoothly with camphorsulfonic acid (CSA) and Amberlyst-15 (Table 1). Stereochemistry at the quaternary carbon of dione **9** was assigned on the basis of the mechanism and was supported by the NOESY spectrum. To confirm the stereostructure, diketone **9** was transformed into a crystalline derivative. Thus, the reaction of diketone **9** with *p*-toluenesulfonyl hydrazide furnished the hydroxypyrazole derivative **10** (Scheme 4), whose single crystal X-ray diffraction analysis, Figure 1, unambiguously established the stereostructure of diketone **9**.

In order to obtain the other diastereoisomer of **9**, the reaction was carried out with the *syn*-epoxide **11**, which was obtained by hydroxy directed epoxidation of allyl alcohol **12**. Thus, the stereoselective reduction[6] of β-methylcarvone **7** with lithium aluminium hydride (LAH) at low temperature furnished the *syn*-allyl alcohol **12**. Reaction of allyl alcohol **12** with *m*-chloroperbenzoic acid (*m*-CPBA) in methylene chloride furnished the epoxyalcohol **13** in a regio- and stereoselective manner, which on oxidation with pyridinium chlorochromate (PCC) and sodium acetate in methylene chloride generated the *syn*-epoxide **11**. As anticipated, the reaction of *syn*-epoxide **11** with an excess of *p*-TSA in methylene chloride at room temperature for 8 h furnished β-diketone **14** in 65% yield along with a trace amount of epimeric β-diketone **9**. Conversely, the reaction of the epoxide **11** with Amberlyst-15 in methylene chloride was found to be very clean and furnished β-diketone **14** in 78% yield in a highly stereoselective manner. The results are summarised in Table 1.

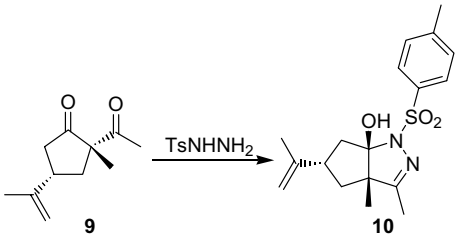


Scheme 3. Reagents and conditions: (a) (i) MeMgI, Et_2O, 0 °C → rt, 1 h; (ii) PCC, silica gel, CH_2Cl_2, rt 4 h; (b) 30% H_2O_2, 6 N NaOH, MeOH, 6 h; (c) see Table 1; (d) LAH, Et_2O, −70 °C, 1 h; (e) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C → rt, 2 h; (f) PCC, NaOAc, CH_2Cl_2, rt, 3 h.

Table 1. Reactions of the ketoepoxides **8** and **11**

Entry	Epoxide	Reaction conditions	Products (yield, %)
a	**8**	*p*-TSA, rt, CH_2Cl_2, 4.5 h	**9** (74)
b	**8**	Amberlyst-15, CH_2Cl_2, rt, 10 h	**9** (65)
c	**8**	CSA, CH_2Cl_2, rt, 24 h	**9** (73)
d	**11**	*p*-TSA, rt, CH_2Cl_2, 8 h	**14** (65)[a]
e	**11**	Amberlyst-15, CH_2Cl_2, rt, 13 h	**14** (78)
f	**8**	$TiCl_4$, CH_2Cl_2, −70 → 0 °C, 3 h	**15** (35), **16** (34)
g	**11**	$TiCl_4$, CH_2Cl_2, −70 → 0 °C, 3 h	**17** (78)
h	**8**	$BF_3{\cdot}Et_2O$, CH_2Cl_2, −70 °C, 4 h	**9** (60), **14** (29)
i	**8**	$BF_3{\cdot}Et_2O$, CH_2Cl_2, −70 °C → rt, 7 h	**9** (20), **14** (10), **18** (35)
j	**8**	$BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C → rt, 14 h	**9** (51), **14** (22), **18** (12)
k	**11**	$BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C → rt, 3 h	**9** (24), **14** (70)

[a] Minor amount (≈5%) of the dione **9** was also obtained.



Scheme 4.

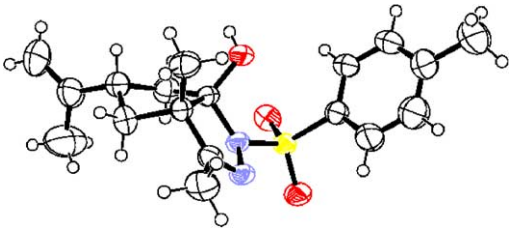
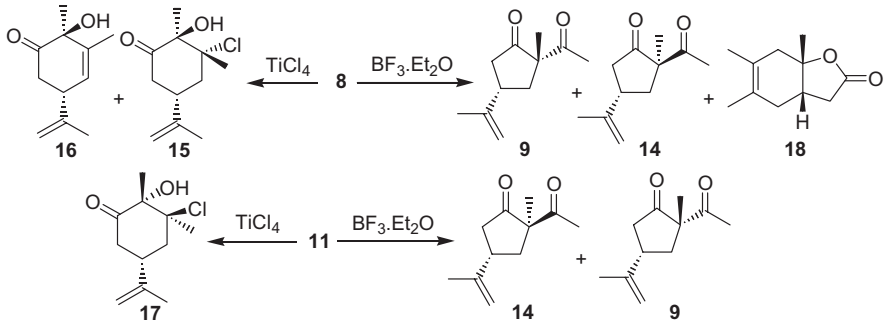


Figure 1. ORTEP of the sulfonamide **10**.

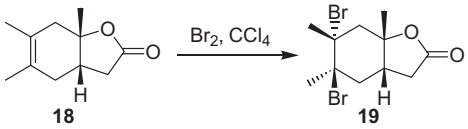
Next, reactions were explored with Lewis acids. Reaction of epoxides **8** and **11** with titanium tetrachloride failed to generate the β-diketones **9** and **14** (Scheme 5). Treatment of *anti*-epoxide **8** with 30 mol % of titanium tetrachloride furnished a 1:1 mixture of chlorohydrin **15** and allyl alcohol **16** in 70% yield. Conversely, the reaction of *syn*-epoxide **11** under the same conditions furnished cleanly chlorohydrin **17**, mp 77–79 °C, in 78% yield, whose structure was confirmed by single crystal X-ray diffraction analysis.[7] On the other hand, in contrast to the literature reports,[1,8] the reaction of *anti*-epoxide **8** with boron trifluoride etherate was found to be nonstereoselective and temperature dependent. For example, treatment of epoxide **8** with 1 equiv of boron trifluoride etherate in methylene chloride at −70 °C for 4 h furnished a 2:1 mixture of diketones **9** and **14**. On the other hand, the addition of boron trifluoride etherate at −70 °C and then allowing the reaction to reach room temperature over a period of 7 h furnished an unusual product, lactone **18** in 35% yield, along with 30% yield of a 2:1 mixture of the diketones **9** and **14**. However, the addition of 30 mol % of boron trifluoride etherate at 0 °C and then carrying out the reaction at room temperature for 14 h furnished diketones **9** and **14**, and lactone **18** in 51, 22 and 12% yields, respectively. In a similar manner, the reaction of *syn*-epoxide **11** with 30 mol % of boron trifluoride etherate in methylene chloride furnished diketones **9** and **14** in 94% yield in 1:3 ratio. Results are summarised in Table 1. Formation of both diketones **9** and **14** from the epoxides **8** and **11** with boron trifluoride etherate indicates that the reaction proceeds through a carbonium ion, and the anchimeric assistance of the isopropenyl group also plays a crucial role in the product distribution.

The structure of lactone **18** was deduced from its spectral data, in particular, the presence of a carbonyl absorption band at 1773 cm^{-1} in the IR spectrum, the lactone carbon resonance at δ 175.3 in the ^{13}C NMR spectrum and analysis of the ^1H NMR spectrum. In order to confirm the structure of lactone **18**, it was treated with 1 equiv of bromine to furnish dibromide **19**



Scheme 5.

(Scheme 6). Single crystal X-ray diffraction analysis (Fig. 2) of dibromide **19** unambiguously established the structure of lactone **18**.



Scheme 6.

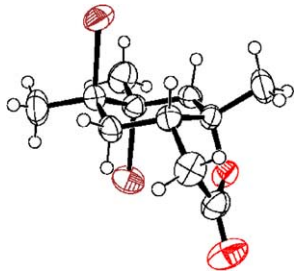


Figure 2. ORTEP diagram of **19**.

The formation of lactone **18** from *anti*-epoxide **8**, obviously, involves a deep-seated rearrangement. A probable mechanism is depicted in Scheme 7. Intramolecular nucleophilic attack of the isopropenyl olefin on to boron trifluoride coordinated epoxide in **8** from the *anti* face furnishes the bicyclo[2.2.2]octyl carbonium ion **20**. Intramolecular addition of oxygen to ketone group followed by ring cleavage and trapping of the carbonium ion by the resultant carboxylate **21** furnishes lactone **18**. The mechanism is partially supported by the absence of a similar product under identical conditions from epoxide **11**, which contains the epoxy oxygen and the isopropenyl group on the same side.

3. Conclusion

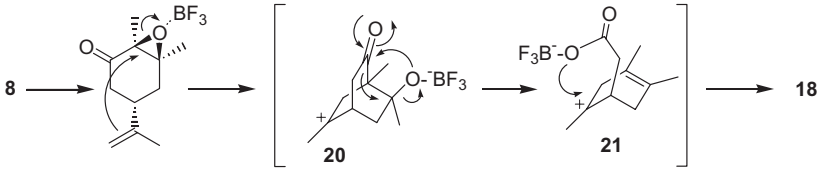
In conclusion, we have developed a convenient enantioselective route to 2-acetylcyclopentanones containing a stereodefined quaternary carbon atom starting from the readily and abundantly available monoterpene (*R*)-carvone, while also observing a novel rearrangement.

4. Experimental

Melting points are recorded using Tempo and Mettler FP1 melting point apparatus in capillary tubes and are uncorrected. IR spectra were recorded on a Jasco FTIR 410 spectrophotometer. ^{1}H (300 MHz) and ^{13}C (75 MHz) spectra were recorded on JNM λ-300 spectrometer. Samples were prepared using a 1:1 mixture of $CDCl_3$ and CCl_4 as solvent for recording the NMR spectra. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) were determined by recording the DEPT-135 and are given in parentheses. Low-resolution mass spectra were recorded using a Shimadzu QP-5050A GC–MS instrument using a direct inlet (EI) mode. Relative intensities are given in parentheses. High resolution mass spectra were recorded on a Micromass Q-TOF micro mass spectrometer using electron spray ionization mode. Optical rotations were measured using a Jasco DIP-370 digital polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Acme's silica gel (100–200 mesh) was used for column chromatography (approximately 15–20 g per 1 g of the crude product). Dry ether was obtained by distillation over sodium and stored over sodium wire. Dry methylene chloride was prepared by distilling over calcium hydride. All the commercial reagents were used as such without further purification.

4.1. 3-(3-Hydroxy-4-methylphenyl)-1,1,3,5-tetramethylindan-4-ol 4 and 1-(3-hydroxy-4-methylphenyl)-1,3,3,6-tetramethylindan-5-ol 4

To a magnetically stirred solution of carvone epoxide **2** (40 mg, 0.24 mmol) in dry benzene (2.4 mL, 0.1 M) was added Amberlyst-15 (40 mg) and refluxed for 2.5 h. The reaction mixture was cooled and the resin filtered off using a sintered funnel. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:30) as eluent furnished, first the minor diol **4** (7 mg, 20% as oil. IR (neat): ν_{max}/cm^{-1} 3521, 1664, 1587. ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 7.04 (1H, d, *J* 7.8 Hz), 7.00 (1H, d, *J* 7.2 Hz), 6.80 (1H, dd, *J* 7.8 and 1.8 Hz), 6.64 (1H, d, *J* 7.2 Hz), 6.63 (1H, d, *J* 1.8 Hz), 4.63 (1H, br s), 4.20 (1H, br s), 2.25 and 2.13 (2H, 2 × d, *J* 13.2 Hz, H-2), 2.20 (3H, s), 2.14 (3H, s), 1.72 (3H, s), 1.34 (3H, s), 1.26 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 154.4 (C), 151.2 (C), 150.1 (C), 147.9 (C), 134.0 (C), 131.5 (CH), 130.9 (CH), 123.1 (C), 122.3 (C), 118.2 (CH), 114.4 (CH), 113.0 (CH), 61.1 (CH_2), 49.6 (C), 43.4 (C), 31.73 (CH_3), 31.68 (CH_3), 27.0 (CH_3), 15.5 (2C, CH_3). Mass: *m*/*z* 296 (M$^+$, 47), 281 (100, M−15), 189 (12), 173 (94), 158 (10), 133 (10), 121 (16). HRMS: *m*/*z* Calcd for $C_{20}H_{24}O_2Na$ (M+Na): 319.1674. Found: 319.1692.



Scheme 7.

Further elution of the column using ethyl acetate–hexane (1:20) as eluent furnished the major diol **3** (28 mg, 78%) as a solid, which was recrystallised from ethanol. Mp: 177–178 °C [lit.[3] mp: 179–180 °C]. IR (neat): ν_{max}/cm^{-1} 3403. ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 6.93 (1H, d, J 7.8 Hz), 6.78 (1H, s), 6.64 (1H, dd, J 7.8 and 1.8 Hz), 6.51 (1H, s), 6.47 (1H, d, J 1.8 Hz), 4.80 (1H, br s), 2.32 and 2.10 (2H, 2 × d, J 12.9 Hz), 2.21 (3H, s), 2.17 (3H, s), 1.58 (3H, s), 1.26 (3H, s), 1.00 (3H, s), 1.43 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 153.5 (C), 153.4 (C), 151.4 (C), 150.8 (C), 140.8 (C), 130.6 (CH), 127.0 (CH), 122.1 (C), 120.6 (C), 119.0 (CH), 113.5 (CH), 108.7 (CH), 59.7 (CH_2), 50.0 (C), 42.7 (C), 31.1 (CH_3), 30.8 (CH_3), 30.5 (CH_3), 16.2 (CH_3), 15.4 (CH_3). Mass: m/z 296 (M$^+$, 19), 281 (100, M–15), 189 (9), 173 (40), 133 (10), 121 (10). HRMS: m/z Calcd for $C_{20}H_{24}O_2Na$ (M+Na): 319.1674. Found: 319.1670. Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 80.81; H, 8.27.

4.2. (−)-(1*S*,4*S*,6*S*)-4-Isopropenyl-1,6-dimethyl-7-oxabicyclo[4.1.0]heptan-2-one 8

To an ice cold, magnetically stirred solution of (*S*)-3-methylcarvone **7** (1 g, 6.1 mmol) in methanol (10 mL) was added 30% aq H_2O_2 (8 mL), followed by a freshly prepared ice cold solution of 6 M aq NaOH (2 mL) dropwise over a period of 20 min. The reaction mixture was stirred for 2 h at the same temperature. It was then diluted with water and extracted with ether (3 × 10 mL). The combined organic extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using CH_2Cl_2–hexane (1:5) as eluent furnished epoxide **8** (856 mg, 78%) as oil.[5] IR (neat): ν_{max}/cm^{-1} 1706, 1646, 893; ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 4.68 (1H, s), 4.63 (1H, s), 2.72–2.55 (1H, m), 2.48 (1H, ddd, J 18.0, 5.1 and 1.5 Hz), 2.13 (1H, dd, J 14.4 and 4.2 Hz), 1.90 (1H, dd, J 18.0 and 12.0 Hz), 1.78 (1H, dd, J 17.4 and 11.7 Hz), 1.65 (3H, s), 1.40 (3H, s), 1.32 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 204.8 (C), 146.4 (C), 110.4 (CH_2), 64.0 (C), 63.4 (C), 41.5 (CH_2), 35.3 (CH_2), 35.0 (CH, C-4), 20.6 (CH_3), 19.6 (CH_3), 11.7 (CH_3).

4.3. (−)-(2*S*,4*S*)-2-Acetyl-4-isopropenyl-2-methylcyclopentanone 9

To a magnetically stirred solution of keto-epoxide **8** (95 mg, 0.53 mmol) in dry CH_2Cl_2 (5.3 mL, 0.1 M) was added Amberlyst-15 (95 mg) and stirred for 10 h at rt. The reaction mixture was then filtered through a small Celite pad. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:50) as eluent furnished diketone **9** (62 mg, 65%) as oil. $[\alpha]_D^{23} = -192.9$ (c 1.82, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1741, 1704, 1648, 894. ^{1}H NMR (400 MHz, $CDCl_3 + CCl_4$): δ 4.84 (1H, s), 4.79 (1H, s), 2.77 (1H, tt, J 12.0 and 5.7 Hz), 2.56–2.45 (2H, m), 2.32 (1H, dd, J 17.6 and 12.0 Hz), 2.24 (3H, s), 1.92 (1H, ddd, J 13.0, 6.2 and 2.0 Hz), 1.79 (3H, s), 1.37 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 214.4 (C), 205.0 (C), 145.3 (C), 110.6 (CH_2), 63.8 (C), 43.6 (CH_2), 39.2 (CH), 37.8 (CH_2), 26.3 (CH_3), 21.1 (CH_3), 20.8 (CH_3). Mass: m/z 180 (M$^+$, 5), 162 (10), 137 (48), 123 (45), 109 (25), 96 (85), 95 (100). HRMS: m/z Calcd for $C_{11}H_{16}O_2Na$ (M+Na): 203.1048. Found: 203.1049.

4.4. (+)-(1*R*,5*S*,7*S*)-7-Isopropenyl-4,5-dimethyl-2-[(4-methylphenyl)sulfonyl]-2,3-diazabicyclo[3.3.0]-oct-3-en-1-ol 10

To a magnetically stirred solution of diketone **9** (18 mg, 0.1 mmol) in dry MeOH (1 mL) was added tosyl hydrazide (47 mg, 0.25 mmol) and refluxed for 2 h. Evaporation of the solvent under reduced pressure followed by purification of the residue on a silica gel column using ethyl acetate–hexane (1:10–1:8) as eluent furnished pyrazole **10** (17 mg, 50%) as a colourless solid, which was recrystallised from a mixture of CH_2Cl_2–hexanes. Mp: 154–155 °C. $[\alpha]_D^{24} = +21.9$ (c 1.51, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3482, 1645, 1598, 892. ^{1}H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 7.83 (2H, d, J 8.4 Hz), 7.28 (2H, d, J 8.4 Hz), 4.68 (1H, s), 4.60 (1H, s), 3.71 (1H, br s), 2.85–2.70 (1H, m), 2.43 (3H, s), 2.39 (1H, ddd, J 12.3, 6.0 and 2.4 Hz), 2.04 (1H, t, J 12.9 Hz), 1.88 (3H, s), 1.78 (1H, ddd, J 12.3, 6.3 and 2.1 Hz), 1.65 (3H, s), 1.54 (1H, t, J 12.3 Hz), 1.15 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 161.4 (C), 145.0 (C), 143.5 (C), 136.6 (C), 129.3 (2C, CH), 128.2 (2C, CH), 110.1 (CH_2), 103.2 (C), 62.0 (C), 46.9 (CH_2), 43.8 (CH), 42.5 (CH_2), 21.7 (CH_3), 21.2 (CH_3), 17.0 (CH_3), 12.8 (CH_3). HRMS: m/z Calcd for $C_{18}H_{23}N_2O_2S$ (M−OH): 331.1474. Found: 331.1474. Anal. Calcd for $C_{18}H_{24}N_2O_3S$: C, 62.07; H, 6.89; N, 8.04; S, 9.19. Found: C, 62.18; H, 6.83; N, 7.99; S, 9.14.

4.5. Crystal data for 10

X-ray data were collected at 293 K on a SMART CCD-BRUKER diffractometer with graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods (SIR92). Refinement was done by full-matrix least-squares procedures on F^2 using SHELXL-97. The nonhydrogen atoms were refined anisotropically whereas hydrogen atoms were refined isotropically. $C_{18}H_{24}N_2O_3S$; MW = 348.45; colourless crystal; crystal system: orthorhombic; space group $P2(1)2(1)2(1)$; cell parameters, $a = 8.5749(23)$ Å, $b = 11.8643(32)$ Å, $c = 18.1951(49)$ Å; $V = 1851.08$ Å^3, $Z = 4$, $\rho = 1.25$ g cm^{-3}, $F(000) = 743.9$, $\mu = 0.192$ mm^{-1}. Total number of l.s. parameters = 222, $R1 = 0.046$ for 3432 $F_o > 4\sigma(F_o)$ and 0.050 for all 3692 data. $wR2 = 0.107$, GOF = 1.138, restrained GOF = 1.138 for all data. An ORTEP diagram of **10** with 50% ellipsoidal probability has been shown in Figure 1. Crystallographic data has been deposited with Cambridge Crystallographic Data Centre (CCDC 260156).

4.6. (+)-(1*R*,4*S*,6*R*)-4-Isopropenyl-1,6-dimethyl-7-oxabicyclo[4.1.0]heptan-2-one 11

To an ice cold, magnetically stirred solution of allyl alcohol **12** (460 mg, 2.80 mmol) in dry CH_2Cl_2 (4 mL) were added solid $NaHCO_3$ (≈50 mg) and 70% MCPBA (70% assay, 820 mg, 3.32 mmol). The reaction mixture was slowly warmed to rt and stirred for 2 h protected

from light. It was then washed with saturated aq Na_2SO_3 solution (5 mL) and extracted with CH_2Cl_2 (3×3 mL). The combined organic extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:20–1:10) as eluent furnished the epoxy alcohol **13** (375 mg, 75%) as oil. $[\alpha]_D^{26} = +24.5$ (*c* 0.98, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3435, 1645, 890. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 4.64 (2H, s), 3.74–3.64 (1H, m), 2.72–2.62 (1H, m), 2.08–1.90 (1H, m), 1.80–1.60 (3H, m), 1.65 (3H, s), 1.36 (3H, s), 1.32 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 147.3 (C), 109.7 (CH_2), 72.4 (CH), 64.9 (C), 64.7 (C), 39.8 (CH), 35.2 (CH_2), 33.6 (CH_2), 21.5 (CH_3), 20.0 (CH_3), 15.1 (CH_3). HRMS: *m/z* Calcd for $C_{11}H_{16}O_2Na$ (M+Na): 203.1048. Found: 203.1047.

To a magnetically stirred solution of epoxy-alcohol **13** (120 mg, 0.66 mmol) in dry CH_2Cl_2 (2 mL) was added finely powdered NaOAc (426 mg, 2.5 equiv to PCC) followed by PCC (426 mg, 1.97 mmol) in portions. The reaction mixture was stirred for 5 h at rt. It was then filtered through a small silica gel column using excess ether. Evaporation of the solvent and rapid purification of the residue on a silica gel column using ethyl acetate–hexane (1:5) as eluent furnished the epoxy ketone **11** (85 mg, 72%) as oil. $[\alpha]_D^{26} = +21.5$ (*c* 1.21, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1714, 1646, 895. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 4.71 (2H, s), 2.83 (1H, dd, *J* 14.1 and 12.3 Hz), 2.60–2.45 (1H, m), 2.12–1.90 (3H, m), 1.70 (3H, s), 1.42 (3H, s), 1.36 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 207.6 (C), 146.0 (C), 110.8 (CH_2), 68.1 (C), 63.8 (C), 43.5 (CH), 39.5 (CH_2), 34.8 (CH_2), 21.3 (CH_3), 19.5 (CH_3), 11.3 (CH_3).

4.7. (−)-(2*R*,4*S*)-2-Acetyl-4-isopropenyl-2-methylcyclopentanone 14

Reaction of keto-epoxide **11** (70 mg, 0.4 mmol) in dry CH_2Cl_2 (4 mL, 0.1 M) with PTSA (380 mg, 2 mmol), as described for diketone **9**, and purification of the product on a silica gel column using ethyl acetate–hexane (1:50) as eluent furnished diketone **14** (45 mg, 65%) as an oil. $[\alpha]_D^{23} = -107.9$ (*c* 1.14, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1742, 1705, 1648, 890. ^1H NMR (400 MHz, $CDCl_3 + CCl_4$): δ 4.80 (1H, s), 4.75 (1H, s), 2.84 (1H, ddd, *J* 12.3, 6.2 and 2.4 Hz), 2.71 (1H, tt, *J* 18.3 and 7.5 Hz), 2.50 (1H, ddd, *J* 18.3, 7.5 and 2.3 Hz), 2.19 (1H, dd, *J* 18.3 and 12.0 Hz), 2.20 (3H, s), 1.77 (3H, s), 1.48 (1H, t, *J* 12.0 Hz), 1.39 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 214.2 (C), 203.9 (C), 145.9 (C), 109.9 (CH_2), 66.0 (C), 42.8 (CH_2), 40.0 (CH), 39.0 (CH_2), 25.6 (CH_3), 21.9 (CH_3), 21.1 (CH_3). Mass: *m/z* 180 (M^+, 3), 138 (15), 137 (30), 123 (27), 109 (12), 96 (50), 95 (60). HRMS: *m/z* Calcd for $C_{11}H_{17}O_2$ (M+1): 181.1228. Found: 181.1228.

4.8. (+)-(2*R*,3*R*,5*R*)-3-Chloro-2-hydroxy-5-isopropenyl-2,3-dimethylcyclohexanone 15 and (−)-(2*S*,5*R*)-2-hydroxy-5-isopropenyl-2,3-dimethylcyclohex-3-enone 16

To a cold (−70 °C), magnetically stirred solution of the keto-epoxide **8** (60 mg, 0.33 mmol) in dry CH_2Cl_2 (3.3 mL, 0.1 M) was added a solution of $TiCl_4$ (0.1 mL, 1 M in CH_2Cl_2, 0.1 mmol). The reaction mixture was then allowed to warm to 0 °C over a period of 3 h and quenched with saturated aq $NaHCO_3$ solution (5 mL). The organic layer was separated, washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using CH_2Cl_2–hexane (1:4) as eluent furnished chlorohydrin **15** (25 mg, 35%) as oil. $[\alpha]_D^{26} = +49.5$ (*c* 3.11, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3480, 1718, 1646, 896. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 4.85 (1H, s), 4.80 (1H, s), 3.92 (1H, br s), 2.71–2.13 (5H, m), 1.78 (3H, s), 1.54 (3H, s), 1.50 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 210.1 (C), 145.0 (C), 111.5 (CH_2), 81.7 (C), 75.3 (C), 44.9 (CH_2), 40.6 (CH_2), 40.3 (CH), 25.6 (CH_3), 24.2 (CH_3), 20.5 (CH_3). Mass: 216 (M^+, 3), 173 (14), 139 (23), 137 (25), 130 (12), 123 (20), 121 (14), 109 (18), 95 (47), 85 (100). HRMS: *m/z* Calcd for $C_{11}H_{17}ClO_2Na$ (M+Na): 239.0815. Found: 239.0810.

Further elution of the column using CH_2Cl_2–hexane (1:1) furnished allyl alcohol **16** (20 mg, 34%) as oil. $[\alpha]_D^{26} = -34.5$ (*c* 1.68, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3486, 1720, 1645, 896. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 5.30 (1H, br s), 4.81 (1H, s), 4.80 (1H, s), 3.57 (1H, s), 3.22–3.13 (1H, m), 2.74 (1H, dd, *J* 12.3 and 10.2 Hz), 2.59 (1H, ddd, *J* 12.3, 6.3 and 0.9 Hz), 1.85 (3H, t, *J* 1.8 Hz), 1.75 (3H, s), 1.46 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 211.0 (C), 146.3 (C), 140.4 (C, C-3), 124.6 (CH), 111.8 (CH_2), 74.8 (C), 46.5 (CH), 39.5 (CH_2), 27.4 (CH_3), 19.7 (CH_3), 17.1 (CH_3). Mass: 181 ($M^+ + 1$, 4), 151 (28), 137 (43), 123 (100), 109 (54), 95 (71). HRMS: *m/z* Calcd for $C_{11}H_{16}O_2Na$ (M+Na): 203.1048. Found: 203.1040.

4.9. (−)-(2*S*,3*S*,5*R*)-3-Chloro-2-hydroxy-5-isopropenyl-2,3-dimethylcyclohexanone 17

Reaction of keto-epoxide **11** (80 mg, 0.44 mmol) in dry CH_2Cl_2 (4.4 mL, 0.1 M) with $TiCl_4$ (0.13 mL, 1 M solution in CH_2Cl_2, 0.13 mmol) for 3 h as described above, and purification on a silica gel column using ethyl acetate–hexane (1:50) as eluent furnished chlorohydrin **17** (75 mg, 78%) as a solid, which was crystallised from hexanes. Mp: 77–79 °C. $[\alpha]_D^{24} = -13.8$ (*c* 3.9, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3473, 1715, 1646, 895. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 4.79 (2H, s), 2.94 (1H, d, *J* 12.9 Hz), 2.90–2.75 (2H, m), 2.60 (1H, br s), 2.41 (1H, dd, *J* 14.0 and 11.7 Hz), 2.27 (1H, m of d, *J* 11.7 Hz), 1.88 (1H, m of d, *J* 14.0 Hz), 1.77 (3H, s), 1.68 (3H, s), 1.45 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 208.3 (C), 146.3 (C), 110.8 (CH_2), 78.5 (C), 74.9 (C), 40.9 (CH_2), 40.44 (CH), 40.41 (CH_2), 26.0 (CH_3), 20.7 (CH_3), 18.1 (CH_3). Mass: *m/z* 183 ($M^+ - H_2O - CH_3$, 3), 149 (18), 139 (20), 137 (27), 123 (26), 109 (28), 95 (46). HRMS: *m/z* Calcd for $C_{11}H_{17}ClO_2Na$ (M+Na): 239.0815. Found: 239.0816. Anal. Calcd for $C_{11}H_{17}ClO_2$: C, 60.97; H, 7.91. Found: C, 60.71; H, 8.02.

4.10. Rearrangement of the epoxide 8 with $BF_3 \cdot Et_2O$

To a cold (−70 °C), magnetically stirred solution of keto-epoxide **8** (90 mg, 0.5 mmol) in dry CH_2Cl_2

(5 mL, 0.1 M) was added a solution of freshly distilled $BF_3{\cdot}Et_2O$ (0.5 mL, 1 M in CH_2Cl_2, 0.5 mmol). The reaction mixture was then allowed to warm to rt over a period of 7 h and the reaction quenched with saturated aq $NaHCO_3$ solution (5 mL). The organic layer was separated, washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using CH_2Cl_2–hexane (1:10) as eluent furnished, first diketones **14** (19 mg, 21%) and diketone **9** (28 mg, 31%) as oils. Further elution of the column using CH_2Cl_2–hexane (1:2) furnished lactone **18** (15 mg, 17%) as oil. $[\alpha]_D^{26} = +58.8$ (*c* 0.97, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1771. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 2.62 (1H, dd, *J* 16.8 and 8.4 Hz), 2.35–2.14 (4H, m), 2.19 (1H, dd, *J* 16.8 and 8.1 Hz), 1.94 (1H, d, *J* 15.3 Hz), 1.66 (6H, s), 1.39 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 175.3 (C), 124.9 (C), 124.2 (C), 85.5 (C), 41.9 (CH_2), 39.8 (CH), 35.9 (CH_2), 34.0 (CH_2), 27.1 (CH_3), 19.4 (CH_3), 19.3 (CH_3). Mass: *m*/*z* 180 (M^+, 31), 165 (29), 162 (25), 137 (29), 123 (30), 121 (51), 120 (30). HRMS: *m*/*z* Calcd for $C_{11}H_{16}O_2Na$ (M+Na): 203.1048. Found: 203.1058.

4.11. (−)-(1*R*,3*R*,4*R*,6*S*)-3,4-Dibromo-3,4,6-trimethyl-7-oxabicyclo[4.3.0]nonane 19

To a magnetically stirred ice cold solution of lactone **18** (20 mg, 0.11 mmol) in dry CCl_4 (3 mL) was added bromine (0.1 mL, excess). The reaction mixture was stirred for 30 min at the same temperature. Excess bromine and the solvent were removed under reduced pressure. Purification of the residue on a silica gel column using ethyl acetate–hexane (1:20) as eluent furnished the dibromide **19** (15 mg, 40%) as a crystalline solid, which was recrystallised from a mixture of CH_2Cl_2–hexanes. Mp: 119–122 °C. $[\alpha]_D^{25} = -15.6$ (*c* 1.22, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1773. ^1H NMR (300 MHz, $CDCl_3 + CCl_4$): δ 2.92 (1H, dd, *J* 17.1 and 7.2 Hz), 2.80–2.65 (1H, m), 2.72 and 2.47 (2H, 2 × d, *J* 16.5 Hz), 2.36–2.25 (1H, m), 2.19 (1H, d, *J* 17.1 Hz), 2.11 (1H, dd, *J* 15.0 and 6.6 Hz), 2.03 (3H, s), 1.99 (3H, s), 1.39 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3 + CCl_4$): δ 159.0 (C), 82.4 (C), 73.3 (C), 65.7 (C), 47.6 (CH_2), 43.1 (CH_2), 38.6 (CH), 35.7 (CH_2), 31.5 (CH_3), 30.5 (CH_3), 27.8 (CH_3). Mass: *m*/*z* 261 and 259 (M^+−Br, 5%), 179 (46), 178 (28), 133 (100), 119 (17), 109 (12), 107 (11), 105 (10). HRMS: *m*/*z* Calcd for $C_{11}H_{16}Br_2O_2K$ (M+K): 376.9154. Found: 376.9155.

4.12. Crystal data for 19

X-ray data were collected at 293 K on a SMART CCD-BRUKER diffractometer with graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 using SHELXL-97. The nonhydrogen atoms were refined anisotropically whereas hydrogen atoms were refined isotropically. $C_{11}H_{16}Br_2O_2$; MW = 340.06; colourless crystal; crystal system: orthorhombic; space group *P*2(1)2(1)2(1); cell parameters, $a = 7.5789(20)$ Å, $b = 9.2141(24)$ Å, $c = 18.4287(47)$ Å; $V = 1286.93(6)$ Å^3, $Z = 4$, $\rho = 1.75$ g cm^{-3}, $F(000) = 671.9$, $\mu = 6.279$ mm^{-1}. Total number of l.s. parameters = 139, $R1 = 0.034$ for 2187 $F_o > 4\sigma(F_o)$ and 0.046 for all 2604 data. $wR2 = 0.080$, GOF = 1.017, restrained GOF = 1.017 for all data. An ORTEP diagram of 19 with 50% ellipsoidal probability has been shown in Figure 2. Crystallographic data has been deposited with Cambridge Crystallographic Data Centre (CCDC 260154).

4.13. Reaction of the keto-epoxide 11 with $BF_3{\cdot}Et_2O$

Reaction of keto-epoxide **11** (90 mg, 0.5 mmol) in dry CH_2Cl_2 (5 mL, 0.1 M) with freshly distilled $BF_3{\cdot}Et_2O$ (0.5 mL, 1 M in CH_2Cl_2, 0.5 mmol) and purification on a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished, first diketone **14** (63 mg, 70%) as oil. Further elution of the column furnished diketone **9** (21 mg, 24%) as oil.

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