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Synthesis of novel spiro-cyclohexene bicyclo[2.2.2]octane derivatives

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Abstract—A methodology for the synthesis of novel spiro-cyclohexene bicyclo[2.2.2]octane derivatives, including Claisen rearrangement and ring-closing metathesis (RCM) as key synthetic steps, is described.

1. Introduction

Spiro-cyclohexane bicyclo[2.2.2]octanes are rarely occurring molecular frameworks, and only a few examples of the synthesis of such systems have been reported so far.[1] The base catalyzed dimerization of substituted cyclohexenones, leading to structurally simple spiro-bicyclics, is one of the earliest reported procedures.[2–4] The Diels–Alder reaction between spirodi-*o*-xylylene and maleic anhydride resulted in a spiro-bicycle, as reported by Errede.[5] More structurally advanced spiro-cyclohexane bicyclo[2.2.2]-octanes were synthesized by Holton et al.[6] In the late 1990s Kuwajima et al. reported, in a number of papers, their studies towards the synthesis of taxane diterpenoidic skeletons.[7–9] These were based on a general cyclization procedure for the construction of the eight-membered B-ring of the tricyclic taxane skeleton. As reported, under certain conditions the cyclization-reaction resulted in the formation of spiro-bicyclic by-products, and in one particular study, they were able to optimize the formation of these spiro-bicycles.[10] Notably, compound **1** (Fig. 1) was found to exhibit multi-drug resistance (MDR) reversing activity with the same potency as verapamil. As far as we know there are only two reports concerning natural products containing the substructure of a spiro-bicyclo[2.2.2]octane unit (isolation from *Daphniphyllum* species).[11,12]

Since the early 1990s our group has been involved in the synthesis of bicyclo[2.2.2]octane compounds, mostly in connection with ligand design and also for other synthetic purposes.[13,14] Recently, we reported the synthesis of spiro-bicycle **3** as a mimetic of paclitaxel.[15] Since this compound was inactive it motivated the incorporation of additional pharmacophores. Thus, we decided to develop a method

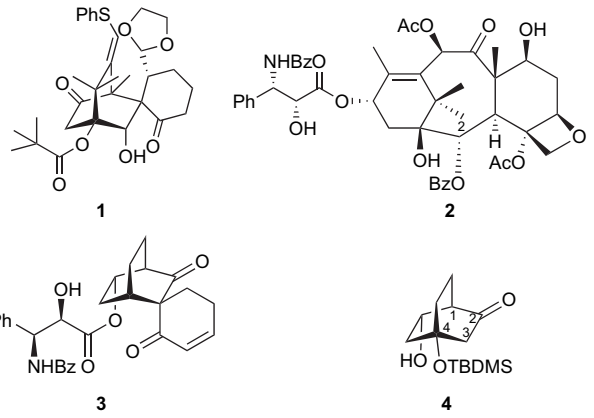

Figure 1.

for the synthesis of bridgehead oxy-functionalized spiro-bicyclo[2.2.2]octanes. As a first step in this direction we developed a synthesis of compound **4**.[16] The initial plan for the spiro-annulation of compound **4** at position 3, was to utilize the same route as employed for the synthesis of compound **3**.[15] However, in the case of the bridgehead silyl-oxy-functionalized derivatives this route was unproductive, and therefore a different methodology had to be developed. Herein, we wish to report our synthetic strategy towards novel bridgehead methoxy substituted spiro-cyclohexene bicyclo[2.2.2]octane derivatives, which includes Claisen rearrangement and ring-closing metathesis (RCM) as key synthetic transformations.

2. Results and discussion

As a first step we decided to protect the 6-OH in **4** as its benzyl ether. For practical reasons we used an 85:15 mixture

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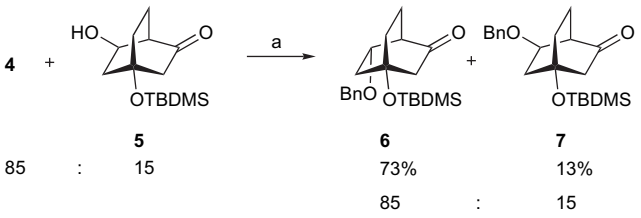
of **4** and **5**, respectively, as starting materials since **4** and **5** were equilibrating under various conditions (Scheme 1).

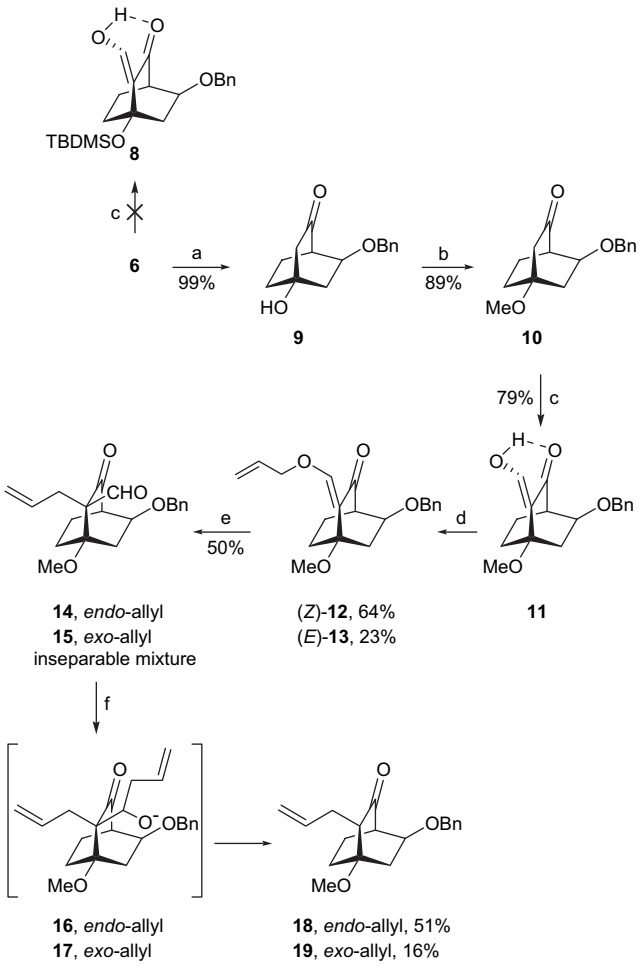


Scheme 1. Benzyl protection of diastereomers **4** and **5**. Reaction conditions: (a) NaH (2.5 equiv), BnBr (2.7 equiv), TBAI (0.5 equiv), THF, 0 °C–rt, 1.5 h.

Endo-alcohol **4** and *exo*-alcohol **5**, were obtained via a ring-closing aldolization reaction as a diastereomeric mixture in a ratio of 85:15, respectively.[16] Compounds **4** and **5** could easily be separated by column chromatography. However, when treated with NaH, a fast ring-opening and -closing occurred, yielding the same ratio of 85:15 diastereomers **6** and **7**, respectively, after the addition of BnBr/TBAI. Diastereomers **6** and **7**, obtained in 86% combined yields, were then separated by column chromatography.

Initial attempts to formylate **6** with ethyl formate, in the presence of NaH, to produce **8**, were unproductive (Scheme 2). This is probably due to the steric hindrance imposed by the large TBDMS protective group positioned at the bridgehead oxygen. We therefore decided to replace the bulky TBDMS group with the much smaller methyl group despite the bad prospect of removing it later. Thus, the TBDMS–ether was cleaved by use of $BF_3 \cdot OEt_2$ in MeCN at 0 °C,[17] which gave bridgehead hydroxyl compound **9** in 99% yield. Methylation of compound **9** was performed by the use of Ag_2O and methyl iodide, which gave methyl ether **10** (89%). Subsequent condensation of compound **10** with ethyl formate produced hydroxymethylenated product **11** in 79% yield.

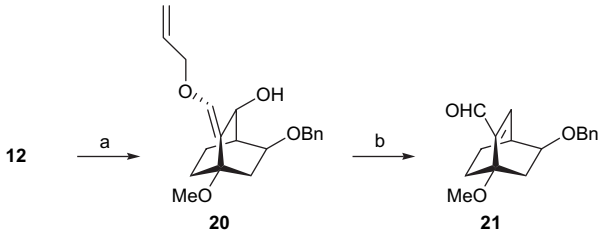
For the attachment of an allyl group at the α-carbon, we planned to employ the Tsuji–Trost reaction,[18] which was reported to give *C*-allylation exclusively.[19] However, when subjecting compound **11** to $Pd(dba)_2/PPh_3$/allyl acetate with NaH as the base, it led to complex reaction mixtures, from which only a small amount of the *O*-allylated derivative **12** was obtained after column chromatography (Scheme 2). This observation made us change strategy, and instead of optimizing the Tsuji–Trost reaction, we decided to perform a Claisen rearrangement[20] of the *O*-allylated product, which ultimately would lead to the same product as expected from the Tsuji–Trost reaction. Thus, compound **11** was subjected to NaH and allyl bromide in THF, which yielded the *O*-allylated products **12** and **13** (75:25) in 87% combined yields (Scheme 2). The mixture of **12** and **13** was then heated at 165 °C in toluene for 12 h and the Claisen rearrangement products **14** and **15** (70:30 as determined by ^1H NMR analysis) were obtained as an inseparable mixture in 50% yield together with 47% combined yield of recovered starting materials **12** and **13**. Even though products **14** and **15** were impossible to be separated by column chromatography, we decided to continue with this mixture of isomers, with the hope to be able to achieve separation at a later stage. Reaction of the aldehyde functionalities of compounds **14** and **15** with allyl Grignard reagent apparently gave the desired allyl-



Scheme 2. Reaction conditions: (a) $BF_3 \cdot OEt_2$ (1 equiv), MeCN, −10 °C, 2 h; (b) MeI (35 equiv), Ag_2O (3.8 equiv), MeCN, 40 °C, 48 h; (c) NaH (3.0 equiv), ethyl formate (10 equiv), THF, 0 °C–rt, 48 h; (d) NaH (2.5 equiv), allyl bromide (2.0 equiv), THF, 50 °C, 4 h; (e) toluene, 165 °C, 12 h (sealed tube); (f) allyl magnesium bromide (1 equiv), THF, −78 °C to rt.

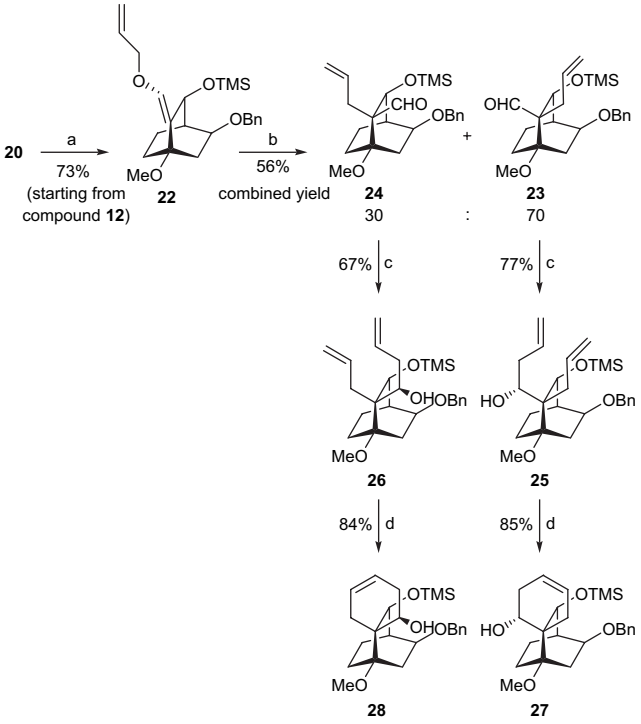
addition products. However, the intermediate homo allylic alcoholates **16** and **17** (shown in brackets in Scheme 2) were unstable. The compounds obtained from this reaction were the mono-allylic derivatives **18** and **19** (67% combined yields, **18/19** 75:25, respectively). Thus, elimination of the homoallylic part had occurred. Attempts were made to try and capture the intermediate alkoxide in situ by addition of TMS–Cl to the allyl Grignard reaction mixture. However, the elimination was too fast at 0 °C, and at lower temperatures (−78 °C) no reaction took place at all. Apparently, the elimination of the homoallylic part of intermediates **16** and **17** involves assistance from the ketone functionality by enolate formation. Accordingly, reduction of the ketocarbonyl group of compound **12** would render the elimination impossible in the following allyl-addition reaction. The same reasoning would, of course, also apply for ketone **13**. However, since this isomer was obtained in minor amounts, we decided to continue the synthesis using only compound **12**. Thus, the ketone functionality of compound **12** was reduced by employing a modified Luche reagent ($NaBH_4/CeCl_3$/2,6-lutidine), which had been applied before by Banwell et al.[21] in a similar situation. The reduction

exclusively afforded *endo*-alcohol **20** (Scheme 3), but when this compound was tested in the Claisen rearrangement reaction, it resulted in the isolation of α,β-unsaturated aldehyde **21**, which was formed together with minor amounts of an unidentified product.



Scheme 3. Reaction conditions: (a) $NaBH_4$ (2.0 equiv), $CeCl_3$ (2.0 equiv), 2,6-lutidine, EtOH (95%), 0 °C, 1 h and (b) toluene, 165 °C, 12 h (sealed tube).

Apparently, formation of **21** from **20** (Scheme 3) involved some kind of elimination of allylic alcohol, which may occur via proton induced removal of water followed by hydrolysis. To circumvent the formation of unwanted product **21**, crude alcohol **20** was TMS protected to give compound **22** (73% yield, starting from **12**) (Scheme 4), which in turn was subjected to Claisen rearrangement conditions (165 °C in toluene). This resulted in the formation of the desired allyl-aldehydes **23** and **24** (56% combined yields). In this case, the starting material, compound **22**, was fully consumed after 20 h, in contrast to the reaction when performed with ketones **12** and **13**, as mentioned. The modest yield obtained of compounds **23** and **24** (56%) can be ascribed to the formation of several unidentified by-products.



Scheme 4. Synthesis of spiro-bicycles **27** and **28**. Reaction conditions: (a) TMSCl (2.5 equiv), Et_3N (2.5 equiv), DMAP (cat.), CH_2Cl_2, 0 °C, 0.5 h; (b) toluene, 165 °C, 20 h (sealed tube); (c) allyl magnesium bromide (2 equiv), THF, 0 °C, 1.5 h and (d) [$RuCl_2$(=CHPh)(PCy_3)$_2$] (10 mol %), CH_2Cl_2, 40 °C, 10 h.

After separation by column chromatography, compounds **23** and **24** (ratio: 70:30, respectively) were reacted separately in subsequent transformations. Thus, by subjecting **23** and **24** to allyl Grignard reagent in THF at 0 °C, homoallylic alcohols **25** and **26** were obtained in 77% and 67% yields, respectively. The diastereoselectivity of this reaction turned out to be high, as only one diastereomer was isolated in each case, as indicated by ^{1}H NMR analysis. The last step in the reaction sequence consisted of a ring-closing metathesis reaction,[22,23] which progressed nicely, affording spirocyclohexene bicyclo[2.2.2]octanes **27** and **28** in 85% and 84% yields, respectively.

The structure of target molecule **27** was confirmed by single-crystal X-ray analysis (Fig. 2 and Supplementary data), which revealed the hydroxyl group, positioned at the spiro-ring, to have an *endo*-configuration (in relation to the bicyclic framework).

The structure of product **27** could also be established on the basis of 2D-NMR experiments (COSY and NOESY). Specifically, the absence of a W-coupling between protons Ha-6′ and H-2′ in the COSY spectrum of compound **27** (Fig. 3a) again established the spiro-hydroxyl to have an *endo*-configuration.

Unfortunately, we were unable to find a suitable solvent-system for the crystallization of compound **28**, and therefore single-crystal X-ray diffraction could not be carried out in order to confirm its structure. Instead, COSY and NOESY spectroscopies were used for this purpose. Thus, in the case of compound **28**, the characteristic correlation between protons Ha-6′ and H-2′ in the COSY spectrum (W-coupling shown in red in Fig. 3b), indicated the spiro-hydroxyl to have an *exo*-configuration.

It should be pointed out that compound **4** can be obtained in an optically pure state, but that method must be optimized in order to be adaptable to a larger scale.[25] Thus, it is in principle possible to install two adjacent quarternary stereogenic carbon centres in **27** and **28**, although at present not in

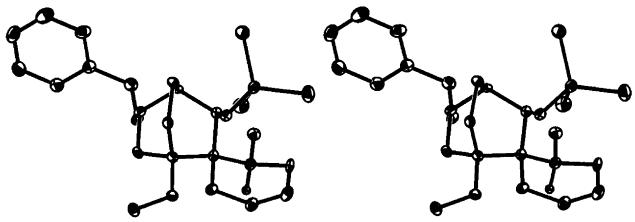


Figure 2. DIAMOND[24] drawing of compound **27**, shown in stereo view. For clarity, all hydrogen atoms, except for the one on C-2′ (see Fig. 3), have been omitted. Thermal ellipsoids are shown at the 30% probability level.

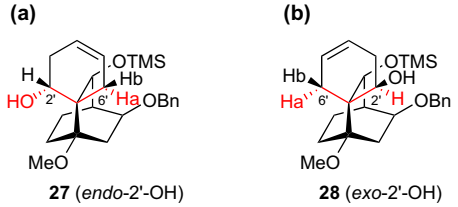


Figure 3.

a highly diastereoselective manner. This demands further investigations and optimizations.

3. Conclusions

We have shown that spirocyclization starting from **4** is a non-selective but yet viable route to spiro-bicyclic compounds **27** and **28**. These compounds contain four hydroxyl groups of which three are protected with orthogonal protective groups, which make them attractive for further transformations. Furthermore, another quarternary carbon centre was installed next to the one already present in **4**.

4. Experimental

4.1. (±)-6-*endo*-Benzyloxy-4-(*tert*-butyl-dimethyl-silyloxy)-bicyclo[2.2.2]octan-2-one (6) and (±)-6-*exo*-benzyloxy-4-(*tert*-butyl-dimethyl-silyloxy)-bicyclo[2.2.2]octan-2-one (7)

NaH (60% in mineral oil, 1.74 g, 43.5 mmol) was added to a solution of **4** and **5** (85:15, respectively)[16] (4.70 g, 17.4 mmol) in dry THF (30 mL) at 0 °C. After 20 min of stirring, TBAI (3.20 g, 8.70 mmol) and BnBr (2.70 mL, 47.0 mmol) were added. Stirring was continued at 0 °C for 5 min and then at rt for 1.5 h. The reaction mixture was again cooled to 0 °C, and water (5 mL) was added dropwise. The water phase was then extracted with EtOAc (3×10 mL), and the combined organic phases were washed with brine and dried. After concentration at reduced pressure, the residue was purified by column chromatography (SiO_2, pentane/ether 9:1) to give **6** (4.60 g, 12.7 mmol, 73%) and **7** (810 mg, 2.25 mmol, 13%) as colourless oils. Compound **6** crystallized upon standing at 4 °C. For compound **6**: mp: 45.7–48.2 °C; IR (KBr) 2938, 2872, 1720 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.36–7.26 (m, 2H) 7.13–7.06 (m, 3H) 4.40 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.16 (dAB, J_{AB}=11.9 Hz, 1H) 3.40–3.36 (m, 1H) 2.60–2.53 (m, 2H) 2.29–2.24 (m, 1H) 1.88–1.79 (m, 2H) 1.31–1.24 (m, 3H) 0.98–0.92 (m, 1H) 0.91 (s, 9H) –0.03 (s, 6H); ^{13}C NMR (100 MHz, benzene-d_6) δ 208.4, 128.6, 128.1, 127.9, 127.5, 74.4, 72.2, 70.0, 52.5, 46.2, 43.01, 33.0, 25.9, 18.3, 18.0, −2.0; HRMS (FAB+) calcd for $C_{21}H_{33}O_3Si$ (M+H): 361.2199. Found: 361.2195. Anal. calcd for $C_{21}H_{32}O_3Si$: C, 69.95; H, 8.95. Found: C, 70.11; H, 8.87. For compound **7**: IR (NaCl) 2955, 2855, 1722 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.21–7.18 (m, 2H) 7.15–7.06 (m, 3H) 4.12 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.02 (d_{AB}, J_{AB}=11.9 Hz, 1H) 3.51–3.47 (m, 1H) 2.57–2.54 (m, 1H) 2.23 (br d_{AB}, J_{AB}=18.1 Hz, 1H) 2.09 (dd_{AB}, J=3.1 Hz, J_{AB}=18.2 Hz, 1H) 2.04–2.01 (m, 1H) 1.77–1.75 (m, 2H) 1.73–1.70 (m, 1H) 1.41–1.35 (m, 1H) 1.27–1.19 (m, 1H) 0.92 (s, 9H) –0.03 (s, 6H); ^{13}C NMR (100 MHz, benzene-d_6) δ 209.1, 138.7, 128.6, 127.9, 127.7, 72.5, 72.1, 70.3, 52.1, 47.0, 43.8, 33.2, 25.8, 18.0, 16.9, −2.0; HRMS (FAB+) calcd for $C_{21}H_{33}O_3Si$ (M+H): 361.2199. Found: 361.2207. Anal. calcd for $C_{21}H_{32}O_3Si$: C, 69.95; H, 8.95. Found: C, 70.05; H, 8.92.

4.2. (±)-6-*endo*-Benzyloxy-4-hydroxy-bicyclo[2.2.2]-octan-2-one (9)

$BF_3 \cdot OEt_2$ (1.60 mL, 12.7 mmol) was added to a solution of **6** (4.60 g, 12.7 mmol) in MeCN (200 mL) at −10 °C. Stirring was continued at −10 °C for approximately 2 h; where after 0.4 M aq $NaHCO_3$ solution (20 mL) was added. The water phase was extracted with EtOAc (3×100 mL) and the combined organic phases were dried. After concentration at reduced pressure, the residue was purified by column chromatography (SiO_2, heptane/EtOAc 1:1) to give **9** (3.10 g, 12.6 mmol, 99%) as a colourless oil. IR (NaCl) 3408, 2953, 2874, 1720 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.24–7.17 (m, 2H) 7.14–7.06 (m, 3H) 4.35 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.12 (d_{AB}, J_{AB}=11.9 Hz, 1H) 3.35–3.31 (m, 1H) 2.50–2.47 (m, 1H) 2.36 (br d_{AB}, J_{AB}=17.9 Hz, 1H) 2.07 (dd_{AB}, J=3.3 Hz, J_{AB}=17.9 Hz, 1H) 1.74–1.70 (m, 1H) 1.59–1.56 (m, 1H) 1.28–1.20 (m, 1H) 1.17–1.12 (m, 2H) 0.93–0.90 (m, 1H) 0.87 (s, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 208.6, 138.6, 128.6, 128.1, 127.9, 127.5, 74.3, 69.8, 69.3, 51.9, 46.3, 42.2, 32.2, 18.2; HRMS (FAB+) calcd for $C_{15}H_{19}O_3$ (M+H): 247.1334. Found: 247.1328. Anal. calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.21; H, 7.34.

4.3. (±)-6-*endo*-Benzyloxy-4-methoxy-bicyclo[2.2.2]-octan-2-one (10)

For the methyl protection, it was important to use commercial Ag_2O, since the yield was low (40%) when we used a home-made quality. MeI (28.0 mL, 445 mmol) and Ag_2O (11.0 g, 47.3 mmol) were added to a solution of **9** (3.10 g, 12.6 mmol) in MeCN (60 mL). The resulting mixture was stirred at 40 °C for 48 h. The reaction mixture was then allowed to cool to rt, and filtered through a pad of Celite, which was rinsed with EtOAc. After concentration at reduced pressure, the resulting residue was purified by column chromatography (SiO_2, heptane/EtOAc 75:25) to give **10** (2.91 g, 11.2 mmol, 89%) as a slightly yellow oil. IR (NaCl) 2953, 2876, 1732 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.25–7.24 (m, 2H) 7.14–7.06 (m, 3H) 4.38 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.14 (d_{AB}, J_{AB}=11.9 Hz, 1H) 3.39–3.35 (m, 1H) 2.83 (s, 3H) 2.52–2.47 (m, 2H) 2.21–2.15 (m, 1H) 1.82–1.79 (m, 1H) 1.75–1.68 (m, 1H) 1.29–1.22 (m, 3H) 0.97–0.91 (m, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 208.3, 138.6, 128.6, 128.1, 127.9, 127.5, 74.2, 74.0, 69.9, 49.2, 47.5, 46.3, 38.1, 28.7, 18.0; HRMS (FAB+) calcd for $C_{16}H_{21}O_3$ (M+H): 261.1491. Found: 261.1490. Anal. calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.74; H, 7.67.

4.4. (±)-6-*endo*-Benzyloxy-3-hydroxymethylene-4-methoxy-bicyclo[2.2.2]octan-2-one (11)

Compound **10** (2.31 g, 8.89 mmol), dissolved in THF (15 mL), was added drop wise to a solution of NaH (60% in mineral oil, 1.10 g, 26.7 mmol) in dry THF (70 mL) at 0 °C. Stirring was continued for 20 min at 0 °C and then ethyl formate (7.20 mL, 88.9 mmol) was added drop wise. Stirring was continued for 5 min at 0 °C and then at rt for 48 h. After cooling to 0 °C, the reaction mixture was quenched by slow addition of 2 M aq H_2SO_4 (80 mL). The organic phase was separated and the water phase extracted with EtOAc (3×80 mL). The combined organic phases were then washed with brine and dried. After concentration at reduced pressure, the residue was purified by column chromatography (SiO_2, heptane/EtOAc 85:15) to give **11**

(2.03 g, 7.04 mmol, 79 %) as a colourless oil. IR (NaCl) 2955, 2874, 1666, 1597 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.37 (s, 1H) 7.25–7.23 (m, 2H) 7.13–7.06 (m, 3H) 4.39 (d_{AB}, J_{AB}=12.1 Hz, 1H) 4.17 (d_{AB}, J_{AB}=12.1 Hz, 1H) 3.37 (dt, J=9.3, 3.1 Hz, 1H) 2.87 (s, 3H) 2.65–2.63 (m, 1H) 1.80 (dd_{AB}, J=9.1 Hz, J_{AB}=12.8 Hz, 1H) 1.64 (td_{AB}, J=2.9 Hz, J_{AB}=12.8 Hz, 1H) 1.30–1.22 (m, 2H) 1.19–1.14 (m, 1H) 0.97–0.88 (m, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 203.3, 158.9, 138.6, 128.6, 128.1, 127.9, 127.8, 127.5, 117.1, 74.7, 74.5, 69.8, 50.2, 45.1, 39.2, 28.9, 18.6; HRMS (FAB+) calcd for $C_{17}H_{21}O_4$ (M+H): 289.1440. Found: 289.1452. Anal. calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.94; H, 6.91.

4.5. (±)-(*Z*)-3-Allyloxymethylene-6-*endo*-benzyloxy-4-methoxy-bicyclo[2.2.2]octan-2-one (12) and (±)-(*E*)-3-allyloxymethylene-6-*endo*-benzyloxy-4-methoxy-bicyclo[2.2.2]octan-2-one (13)

Compound **11** (1.74 g, 6.04 mmol), dissolved in THF (10 mL), was added drop wise to a solution of NaH (60% in mineral oil, 605 mg, 15.1 mmol) in THF (10 mL) at 0 °C. Stirring was continued for 20 min at 0 °C before ally bromide (1.10 mL, 12.1 mmol) was added. The reaction mixture was then kept at 50 °C for 4 h, after which the reaction mixture was allowed to cool to rt, before being quenched with water (10 mL) at 0 °C. The organic phase was separated, and the water phase saturated with NaCl before being extracted with EtOAc (5×10 mL). The combined organic phases were then washed with brine and dried. After concentration at reduced pressure, the residue was purified by column chromatography (SiO_2, heptane/EtOAc 7:3) to give compound **12** (1.26 g, 3.84 mmol, 64%) as a yellow solid and compound **13** (456 mg, 1.39 mmol, 23%) as a yellow oil. For compound **12**: mp 61.1–65.2 °C; IR (KBr) 2941, 2876, 1693, 1618 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.35 (s, 1H) 7.31–7.29 (m, 2H) 7.13–7.05 (m, 3H) 5.47–5.40 (m, 1H) 5.01–4.95 (m, 1H) 4.87–4.84 (m, 1H) 4.51 (d_{AB}, J_{AB}=12.0 Hz, 1H) 4.24 (d_{AB}, J_{AB}=12.0 Hz, 1H) 3.74–3.71 (m, 2H) 3.53–3.49 (m, 1H) 3.27 (s, 3H) 2.76–2.75 (m, 1H) 2.24 (td_{AB}, J=2.9 Hz, J_{AB}=13.1 Hz, 1H) 1.95 (dd_{AB}, J=9.4 Hz, J_{AB}=13.1 Hz, 1H) 1.85–1.77 (m, 1H) 1.53–1.44 (m, 1H) 1.40–1.33 (m, 1H) 1.14–1.06 (m, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 199.1, 151.6, 138.9, 132.8, 128.5, 128.1, 127.9, 119.1, 118.0, 77.2, 75.1, 74.6, 69.9, 52.5, 46.3, 41.0, 30.6, 18.5; HRMS (FAB+) calcd for $C_{20}H_{24}NaO_4$ (M+Na): 351.1572. Found: 351.1573. Anal. calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.06; H, 7.32. For compound **13**: IR (NaCl) 2951, 2870, 1701, 1616 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.30–7.28 (m, 2H) 7.15–7.06 (m, 3H) 6.63 (s, 1H) 5.58–5.50 (m, 1H) 5.17–5.12 (m, 1H) 4.90–4.87 (m, 1H) 4.53 (d_{AB}, J_{AB}=12.0 Hz, 1H) 4.24 (d_{AB}, J_{AB}=12.0 Hz, 1H) 3.90–3.88 (m, 2H) 3.47 (dt, J=9.4, 3.1 Hz, 1H) 3.00 (s, 3H) 2.76–2.74 (m, 1H) 2.00 (dd_{AB}, J=9.3 Hz, J_{AB}=12.8 Hz, 1H) 1.80 (td_{AB}, J=2.8 Hz, J_{AB}=12.9 Hz, 1H) 1.51–1.34 (m, 3H) 1.07–0.99 (m, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 194.6, 150.9, 139.0, 133.3, 128.5, 128.1, 127.9, 118.6, 117.7, 75.7, 75.1, 74.4, 69.8, 50.0, 47.0, 39.5, 29.0, 18.4; HRMS (FAB+) calcd for $C_{20}H_{24}NaO_4$ (M+Na): 351.1572. Found: 351.1574. Anal. calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.08; H, 7.26.

4.6. (±)-2-*endo*-Allyl-5-*endo*-benzyloxy-1-methoxy-3-oxo-bicyclo[2.2.2]octane-2-carbaldehyde (14) and (±)-2-*exo*-allyl-5-*endo*-benzyloxy-1-methoxy-3-oxo-bicyclo[2.2.2]octane-2-carbaldehyde (15)

Compounds **12** and **13** (276 mg, 0.84 mmol, **12/13** 75:25, respectively) dissolved in toluene (5 mL) were placed in a sealed pressurized vessel and heated at 165 °C for 12 h. After concentration at reduced pressure, the residue was purified by column chromatography (SiO_2, heptane/EtOAc 7:3) to give an inseparable diastereomeric mixture of compounds **14** and **15** (138 mg, 0.42 mmol, 50%) as a colourless oil, together with starting materials **12** and **13** (130 mg, 0.40 mmol, 47%). Analysis for the mixture of **14** and **15**: IR (NaCl) 2957, 2878, 2833, 1738, 1705 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{24}NaO_4$ (M+Na): 351.1572. Found: 351.1575. Anal. calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.21; H, 7.32. Selected ^1H NMR signals for compound **14** (400 MHz, benzene-d_6): δ 6.43–6.33 (m, 1H) 4.33 (d_{AB}, J_{AB}=12.0 Hz, 1H) 4.07 (d_{AB}, J_{AB}=12.0 Hz, 1H) 3.26–3.22 (m, 1H) 3.14–3.08 (m, 1H) 3.00–2.94 (m, 1H) 2.74 (s, 3H). Selected ^1H NMR signals for compound **15** (400 MHz, benzene-d_6): δ 6.23–6.12 (m, 1H) 4.25 (d_{AB}, J_{AB}=12.1 Hz, 1H) 4.13 (d_{AB}, J_{AB}=12.1 Hz, 1H) 3.35–3.31 (m, 1H).

4.7. Attempted allyl Grignard addition to aldehydes 14 and 15, leading to (±)-3-*endo*-allyl-6-*endo*-benzyloxy-4-methoxy-bicyclo[2.2.2]octan-2-one (18) and (±)-3-*exo*-allyl-6-*endo*-benzyloxy-4-methoxy-bicyclo[2.2.2]octan-2-one (19)

Allyl magnesium bromide (150 μL, 1.0 M in Et_2O) was added to a solution of **14** and **15** (70:30, respectively, 50.0 mg, 150 μmol) in THF (1 mL) at −78 °C. The temperature was then slowly allowed to reach rt, where after H_2O (1 mL) was added the organic phase was separated; the water phase extracted with CH_2Cl_2 (3×2 mL), and the combined organic phases were dried. After concentration at reduced pressure the residue was purified by column chromatography (SiO_2, pentane/ether 8:2) to yield compound **18** (23.0 mg, 76.6 μmol, 51%) and compound **19** (7.0 mg, 23.3 μmol, 16%) as colourless oils. For compound **18**: ^1H NMR (400 MHz, benzene-d_6) δ 7.24–7.22 (m, 2H) 7.14–7.05 (m, 3H) 6.46–6.35 (m, 1H) 5.18–5.13 (m, 1H) 5.08–5.05 (m, 1H) 4.35 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.12 (d_{AB}, J_{AB}=11.9 Hz, 1H) 3.34–3.31 (m, 1H) 2.84 (s, 3H) 2.76–2.69 (m, 1H) 2.63–2.56 (m, 1H) 2.52–2.46 (m, 1H) 2.28–2.24 (m, 1H) 1.91 (br d_{AB}, J_{AB}=14.2 Hz, 1H) 1.74 (br ddd_{AB}, J=2.1, 9.4 Hz, J_{AB}=14.2 Hz, 1H) 1.31–1.10 (m, 3H) 0.97–0.89 (m, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 211.2, 138.8, 138.6, 128.6, 127.9, 127.8, 115.1, 75.6, 74.5, 69.8, 55.0, 48.9, 46.6, 35.4, 30.9, 28.0, 17.5; HRMS (FAB+) calcd for $C_{19}H_{25}O_3$ (M+H): 301.1804. Found: 301.1803. For compound **19**: ^1H NMR (400 MHz, benzene-d_6) δ 7.26–7.24 (m, 2H) 7.14–7.06 (m, 3H) 6.34–6.27 (m, 1H) 5.17–5.13 (m, 1H) 5.04–5.01 (m, 1H) 4.38 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.14 (d_{AB}, J_{AB}=11.9 Hz, 1H) 3.38 (dt, J=9.3, 3.1 Hz, 1H) 2.83 (s, 3H) 2.56–2.38 (m, 4H) 1.78 (td_{AB}, J=2.9 Hz, J_{AB}=13.4 Hz, 1H) 1.71 (dd_{AB}, J=9.2 Hz, J_{AB}=13.3 Hz, 1H) 1.55–1.47 (m, 1H) 1.32–1.13 (m, 2H) 1.01–0.93 (m, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 211.5, 138.6, 138.5, 128.6, 128.1, 127.9, 115.4, 76.0, 73.9, 70.0, 54.2,

49.2, 46.6, 38.3, 30.1, 25.6, 18.5; HRMS (FAB+) calcd for $C_{19}H_{25}O_3$ (M+H): 301.1804. Found: 301.1818.

4.8. (±)-(3-Allyloxymethylene-6-*endo*-benzyloxy-4-methoxy-bicyclo[2.2.2]oct-2-*endo*-yloxy)-trimethylsilane (22)

$NaBH_4$ (220 mg, 5.78 mmol) was added to a solution of dry-$CeCl_3$ (1.42 g, 5.78 mmol) in EtOH (99.5%, 60 mL) at 0 °C. After 0.5 h a solution of compound **12** (950 mg, 2.89 mmol) in EtOH (99.5%, 30 mL) and 2,6-lutidine (5.72 mL, 49.1 mmol) was added drop wise, and after 1 h of additional stirring at 0 °C, H_2O (260 μL) was added. The reaction mixture was then directly filtered through a pad of SiO_2 and Celite, and the product was eluted (heptane/EtOAc 1:1). After concentration at reduced pressure, crude alcohol **20** was collected as a slightly yellow oil, and was used directly in the following step. A small sample was purified for analytical purposes (SiO_2, heptane/EtOAc 85:15+10% Et_3N). IR (NaCl) 3512, 2947, 2872 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.20–7.18 (m, 2H) 7.14–7.04 (m, 3H) 6.43 (s, 1H) 5.75–5.65 (m, 1H) 5.24–5.18 (m, 1H) 5.00–4.96 (m, 1H) 4.37–4.33 (m, 1H) 4.23 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.14 (d_{AB}, J_{AB}=11.9 Hz, 1H) 3.94–3.90 (m, 2H) 3.89 (s, 1H) 3.59–3.56 (m, 1H) 3.40 (s, 3H) 2.29 (td_{AB}, J=3.1 Hz, J_{AB}=13.0 Hz, 1H) 2.12–2.09 (m, 1H) 1.87 (dd_{AB}, J=9.2 Hz, J_{AB}=13.0 Hz, 1H) 1.80–1.72 (m, 1H) 1.25–1.18 (m, 2H) 1.06–0.97 (m, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 142.8, 134.5, 128.7, 128.1, 128.0, 127.9, 120.4, 116.6, 78.8, 76.6, 73.6, 73.4, 70.3, 52.0, 40.9, 36.9, 29.3, 20.1; HRMS (FAB+) calcd for $C_{20}H_{26}O_4$ (M): 330.1831. Found: 330.1821. Et_3N (1.0 mL, 7.23 mmol), DMAP (cat.) and TMSCl (925 μL, 7.23 mmol) were added to a solution of crude alcohol **20** in CH_2Cl_2 (23 mL) at 0 °C. Stirring was continued for 0.5 h, and then the solvent was removed at reduced pressure and replaced with cold pentane. The resulting mixture was filtered through Hyflo-Supercel. After concentration at reduced pressure the residue was purified by column chromatography (SiO_2, heptane/EtOAc 9:1) to give TMS/ether **22** (849 mg, 2.11 mmol, 73% starting from compound **12**) as a colourless oil. IR (NaCl) 2949, 2868 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.45–7.43 (m, 2H) 7.26–7.22 (m, 2H) 7.12–7.11 (m, 1H) 6.09 (d, J=1.2 Hz, 1H) 5.76–5.66 (m, 1H) 5.27–5.21 (m, 1H) 5.03–4.99 (m, 1H) 4.46 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.34 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.29–4.28 (m, 1H) 3.94 (dt, J=5.1, 1.6 Hz, 2H) 3.69–3.64 (m, 1H) 3.42 (s, 3H) 2.53 (ddd_{AB}, J_d=2.9, 5.7 Hz, J_{AB}=12.0 Hz, 1H) 2.06–2.04 (m, 1H) 2.02 (dd_{AB}, J=9.4 Hz, J_{AB}=11.9 Hz, 1H) 1.86–1.78 (m, 1H) 1.50–1.41 (m, 1H) 1.27–1.12 (m, 2H) 0.18 (s, 9H); ^{13}C NMR (100 MHz, benzene-d_6) δ 142.9, 140.1, 134.5, 127.9, 127.6, 127.3, 119.2, 116.8, 77.8, 77.1, 73.7, 73.3, 70.1, 51.9, 39.8, 37.0, 30.8, 21.3, 0.6; HRMS (FAB+) calcd for $C_{23}H_{34}O_4Si$ (M): 402.2226. Found: 402.2223. Anal. calcd for $C_{23}H_{34}O_4Si$: C, 68.62; H, 8.51. Found: C, 68.56; H, 8.49.

4.9. (±)-2-*endo*-Allyl-5-*endo*-benzyloxy-1-methoxy-3-*endo*-trimethylsilanyloxy-bicyclo[2.2.2]octane-2-carbaldehyde (23) and (±)-2-*exo*-allyl-5-*endo*-benzyloxy-1-methoxy-3-*endo*-trimethylsilanyloxy-bicyclo[2.2.2]-octane-2-carbaldehyde (24)

Compound **22** (849 mg, 2.11 mmol) dissolved in toluene (14 mL) was placed in a sealed pressurized vessel and was heated at 165 °C for 20 h, where the reaction mixture was allowed to cool to rt. After concentration at reduced pressure, the residue was purified by column chromatography (SiO_2, heptane/EtOAc 95:5) to give compound **23** (325 mg, 808 μmol, 38%) and **24** (149 mg, 370 μmol, 18%) as colourless oils. For compound **23**: IR (NaCl) 2953, 2876, 1717 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 10.07 (s, 1H) 7.42 (br d, J=7.6 Hz, 2H) 7.23 (br t, J=7.6 Hz, 2H) 7.13–7.09 (m, 1H) 6.14–6.04 (m, 1H) 5.18–5.14 (m, 1H) 5.05–5.02 (m, 1H) 4.92 (br t, J=1.9 Hz, 1H) 4.60 (d_{AB}, J_{AB}=11.7 Hz, 1H) 4.20 (d_{AB}, J_{AB}=11.7 Hz, 1H) 3.60–3.54 (m, 1H) 3.43–3.38 (m, 1H) 3.27–3.21 (m, 1H) 2.77 (s, 3H) 1.98 (br s, 1H) 1.88 (td_{AB}, J=2.9 Hz, J_{AB}=13.6 Hz, 1H) 1.66 (dd_{AB}, J=9.9 Hz, J_{AB}=13.6 Hz, 1H) 1.44–1.36 (m, 1H) 1.20–1.06 (m, 2H) 0.83–0.75 (m, 1H) 0.16 (s, 9H); ^{13}C NMR (100 MHz, benzene-d_6) δ 206.4, 139.7, 137.3, 128.5, 127.9, 127.5, 117.3, 78.7, 76.5, 70.0, 69.1, 59.0, 49.1, 35.5, 32.6, 31.5, 23.1, 20.2, 0.2; HRMS (FAB+) calcd for $C_{23}H_{35}O_4Si$ (M+H): 403.2305. Found: 403.2296. Anal. calcd for $C_{23}H_{34}O_4Si$: C, 68.62; H, 8.51. Found: C, 68.73; H, 8.46. For compound **24**: IR (NaCl) 2955, 2882, 1717 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 10.60 (br d, J=1.1 Hz, 1H) 7.37–7.35 (m, 2H) 7.25–7.22 (m, 2H) 7.13–7.11 (m, 1H) 6.37–6.27 (m, 1H) 5.09–5.04 (m, 2H) 4.37 (d_{AB}, J_{AB}=12.1 Hz, 1H) 4.29 (d_{AB}, J_{AB}=12.1 Hz, 1H) 3.88–3.86 (m, 1H) 3.56–3.52 (m, 1H) 3.11–3.06 (m, 1H) 2.81 (s, 3H) 2.29–2.21 (m, 2H) 1.92–1.90 (m, 1H) 1.87–1.81 (m, 1H) 1.38–1.26 (m, 1H) 1.17–0.92 (m, 3H) 0.08 (s, 9H); ^{13}C NMR (100 MHz, benzene-d_6) δ 203.9, 139.7, 137.8, 127.9, 127.6, 127.4, 116.6, 77.7, 77.6, 77.2, 70.2, 57.7, 49.2, 36.7, 36.4, 34.0, 23.9, 20.7, 0.5; HRMS (FAB+) calcd for $C_{23}H_{35}O_4Si$ (M+H): 403.2305. Found: 403.2301. Anal. calcd for $C_{23}H_{34}O_4Si$: C, 68.62; H, 8.51. Found: C, 68.43; H, 8.44.

4.10. General procedure for the allyl Grignard addition reaction, leading to compounds (±)-1-(2-*endo*-allyl-5-*endo*-benzyloxy-1-methoxy-3-*endo*-trimethylsilanyloxy-bicyclo[2.2.2]oct-2-yl)-but-3-en-1-ol (25) and (±)-1-(2-*exo*-allyl-5-*endo*-benzyloxy-1-methoxy-3-*endo*-trimethylsilanyloxy-bicyclo[2.2.2]oct-2-yl)-but-3-en-1-ol (26)

Allyl magnesium bromide (2 equiv, 1.0 M in Et_2O) was added to a solution of **23** (325 mg, 808 μmol) or **24** (149 mg, 370 μmol) in THF (0.5 mL/0.1 mmol) at 0 °C. The temperature was then slowly allowed to reach rt, where after satd aq NH_4Cl was added. The organic phase was separated, the water phase extracted with EtOAc (×3), and the combined organic phases were dried. After concentration at reduced pressure the residue was purified by column chromatography (SiO_2, heptane/EtOAc 95:5) to yield compound **25** (275 mg, 619 μmol, 77%) or **26** (110 mg, 247 μmol, 67%) as colourless oil. For compound **25**: IR (NaCl) 3566, 2949, 2878 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 7.43 (br d, J=7.6 Hz, 2H) 7.23 (br t, J=7.6 Hz, 2H) 7.14–7.10 (m, 1H) 6.63–6.53 (m, 1H) 6.06–5.96 (m, 1H) 5.19–5.13 (m, 2H) 5.10–5.03 (m, 2H) 4.48 (d_{AB}, J_{AB}=12.1 Hz, 1H) 4.46 (s, 1H) 4.33 (d_{AB}, J_{AB}=12.1 Hz, 1H) 4.06–4.01 (m, 1H) 3.51–3.48 (m, 1H) 3.30–3.24 (m, 1H) 3.01–2.94 (m, 2H) 2.84 (s, 3H) 2.51–2.43 (m, 1H) 2.07 (td_{AB}, J=3.7 Hz, J_{AB}=13.4 Hz, 1H) 1.98–1.95 (m, 1H) 1.92 (d, J=6.4 Hz, 1H) 1.88–1.79 (m, 1H) 1.73 (dd_{AB}, J=10.1 Hz,

J_{AB}=13.4 Hz, 1H) 1.48–1.38 (m, 1H) 1.21–1.14 (m, 1H) 1.06–0.96 (m, 1H) 0.21 (s, 9H); ^{13}C NMR (100 MHz, benzene-d_6) δ 141.0, 137.9, 128.5, 128.1, 127.9, 127.4, 116.8, 115.1, 78.8, 77.3, 75.0, 74.4, 70.1, 52.1, 48.4, 39.2, 37.1, 34.1, 33.2, 24.1, 21.3, 0.8; HRMS (FAB+) calcd for $C_{26}H_{41}O_4Si$ (M+H): 445.2775. Found: 445.2786. Anal. calcd for $C_{26}H_{40}O_4Si$: C, 70.23; H, 9.07. Found: C, 70.29; H, 9.02. For compound **26**: ^{1}H NMR (400 MHz, benzene-d_6) δ 7.39 (br d, J=7.4 Hz, 2H) 7.21 (br t, J=7.5 Hz, 2H) 7.13–7.09 (m, 1H) 6.59–6.48 (m, 1H) 6.15–6.05 (m, 1H) 5.35–5.30 (m, 1H) 5.18–5.15 (m, 1H) 5.11–5.07 (m, 2H) 4.53–4.52 (m, 1H) 4.48 (d_{AB}, J_{AB}=11.6 Hz, 1H) 4.46 (s, 1H) 4.22 (d_{AB}, J_{AB}=11.6 Hz, 1H) 3.92–3.91 (m, 1H) 3.57–3.54 (m, 1H) 3.37–3.32 (m, 1H) 3.04–2.96 (m, 1H) 2.89 (s, 3H) 2.86–2.82 (m, 1H) 2.80–2.74 (m, 1H) 2.03–1.98 (m, 1H) 1.84–1.83 (m, 1H) 1.78–1.72 (m, 1H) 1.34–1.28 (m, 1H) 1.18–1.00 (m, 3H) 0.07 (s, 9H); ^{13}C NMR (100 MHz, benzene-d_6) δ 140.3, 139.4, 135.9, 128.5, 127.8, 127.5, 117.5, 114.5, 80.3, 78.8, 77.4, 75.6, 70.1, 50.4, 48.3, 40.4, 39.0, 37.6, 32.6, 24.7, 20.7, 0.6; HRMS (FAB+) calcd for $C_{26}H_{41}O_4Si$ (M+H): 445.2775. Found: 445.2769.

4.11. General procedure for the ring-closing metathesis reaction, leading to compounds (1*R**,2,1′*R**,3*S**,5*S**,2′*R**)-(±)-spiro[5-*endo*-benzyloxy-1-methoxy-3-*endo*-trimethylsilyloxybicyclo[2.2.2]-octane-2,1′-cyclohex-4′-en]-2′-ol (27) and (1*R**,2,1′*S**,3*S**,5*S**,2′*R**)-(±)-spiro[5-*endo*-benzyloxy-1-methoxy-3-*endo*-trimethylsilyloxybicyclo[2.2.2]-octane-2,1′-cyclohex-4′-en]-2′-ol (28)

Grubb's phosphorylidine catalyst [$RuCl_2$(=CHPh)(PCy_3)$_2$] (10 mol %) was added to a solution of **25** (275 mg, 619 μmol) or **26** (103 mg, 232 μmol) in degassed CH_2Cl_2 (1.6 mL/100 μmol). The reaction mixture was heated in a sealed pressurized vessel at 40 °C for 10 h. After concentration at reduced pressure the residue was purified by column chromatography to give compound **27** (219 mg, 526 μmol, 85%) or **28** (81.5 mg, 196 μmol, 84%) as off-white solids. Compound **27** was crystallized from pentane, which resulted in off-white needles. For compound **27** (SiO_2, heptane/EtOAc 9:1): mp: 79.8–82.8 °C; IR (KBr) 3439, 3022, 2936 cm^{-1}; ^{1}H NMR (400 MHz, benzene-d_6) δ 7.44 (br d, J=7.6 Hz, 2H) 7.25 (br t, J=7.6 Hz, 2H) 7.12–7.11 (m, 1H) 5.82–5.78 (m, 1H) 5.44–5.39 (m, 1H) 4.47 (d_{AB}, J_{AB}=12.3 Hz, 1H) 4.36 (d_{AB}, J_{AB}=12.3 Hz, 1H) 4.37–4.31 (m, 2H) 3.58–3.53 (m, 1H) 3.19–3.14 (m, 1H) 3.02 (s, 3H) 2.52–2.47 (m, 1H) 2.33–2.26 (m, 1H) 2.18–2.10 (m, 1H) 2.03–1.93 (m, 3H) 1.75–1.63 (m, 2H) 1.31–1.23 (m, 1H) 1.18–1.11 (m, 1H) 0.78 (br d, J=3.7 Hz, 1H) 0.18 (s, 9H); ^{13}C NMR (100 MHz, benzene-d_6) δ 140.1, 130.2, 128.4, 127.9, 127.3, 121.2, 77.4, 77.3, 72.2, 70.0, 69.0, 49.5, 49.1, 37.4, 34.6, 33.7, 28.2, 25.2, 21.3, 0.9; HRMS (FAB+) calcd for $C_{24}H_{37}O_4Si$ (M+H): 417.2462. Found: 417.2466. Anal. calcd for $C_{24}H_{36}O_4Si$: C, 69.19; H, 8.71. Found: C, 69.26; H, 8.65. For compound **28** (SiO_2, heptane/EtOAc 85:15): mp: 110.4–113.0 °C; IR (KBr) 3422, 3018, 2959 cm^{-1}; ^{1}H NMR (400 MHz, benzene-d_6) δ 7.38 (br d, J=7.6 Hz, 2H) 7.24 (br t, J=7.6 Hz, 2H) 7.13–7.11 (m, 1H) 5.86–5.84 (m, 1H) 5.73–5.69 (m, 1H) 5.11 (br s, 1H) 4.97 (br s, 1H) 4.35 (d_{AB}, J_{AB}=11.9 Hz, 1H) 4.28 (d_{AB}, J_{AB}=11.9 Hz, 1H) 3.72–3.71 (m, 1H) 3.43–3.38 (m, 1H) 3.01–2.96 (m, 1H) 2.91–2.87 (m, 1H) 2.63 (s, 3H) 2.61–2.56 (m, 1H) 2.20–2.15 (m, 1H) 1.97–1.91 (m, 1H) 1.89 (br s, 1H) 1.52–1.46 (m, 1H) 1.16–0.91 (m, 4H) 0.13 (s, 9H); ^{13}C NMR (100 MHz, benzene-d_6) δ 139.7, 128.5, 127.9, 127.6, 127.2, 122.9, 81.2, 78.8, 77.9, 70.5, 66.6, 48.4, 46.5, 38.0, 35.3, 31.1, 28.9, 22.6, 20.4, 0.7; HRMS (FAB+) calcd for $C_{24}H_{37}O_4Si$ (M+H): 417.2462. Found: 417.2465. Anal. calcd for $C_{24}H_{36}O_4Si$: C, 69.19; H, 8.71. Found: C, 68.80; H, 8.54.

4.12. (±)-5-*endo*-Benzyloxy-1-methoxy-bicyclo-[2.2.2]oct-2-ene-2-carbaldehyde (21)

Compound **20** (17 mg, 51.5 μmol) dissolved in toluene (1 mL) was placed in a sealed pressurized vessel and heated at 165 °C for 12 h. After concentration at reduced pressure, the residue was purified by column chromatography (SiO_2, heptane/EtOAc 85:15) to give **21** (8.0 mg, 24.2 μmol, 47%) as a yellow oil. ^{1}H NMR (400 MHz, benzene-d_6) δ 9.73 (s, 1H) 7.22–7.18 (m, 4H) 7.11–7.08 (m, 1H) 6.75 (d, J=6.4 Hz, 1H) 4.16 (s, 2H) 3.40–3.36 (m, 1H) 3.20 (s, 3H) 2.60–2.56 (m, 1H) 1.73 (dd_{AB}, J=8.4 Hz, J_{AB}=12.6 Hz, 1H) 1.62 (td_{AB}, J=3.1 Hz, J_{AB}=12.6 Hz, 1H) 1.25–1.13 (m, 2H) 0.98–0.90 (m, 1H) 0.88–0.79 (m, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 187.5, 146.4, 146.2, 139.0, 128.6, 127.9, 127.6, 78.2, 77.3, 69.9, 52.3, 39.8, 35.6, 28.7, 20.9; HRMS (FAB+) calcd for $C_{17}H_{21}O_3$ (M+H): 273.1491. Found: 273.1496.

4.13. X-ray crystallographic analysis of compound 27

Crystallization from pentane gave needles of compound **27** suitable for X-ray diffraction. Intensity data were collected at 150 K with an Oxford Diffraction Xcalibur 3 system using ω-scans and Mo Kα (λ=0.71073 Å).[26] CCD data were extracted and integrated using Crysalis RED.[27] The structure was solved by direct methods and refined by full-matrix least-squares calculations on F^2 using SHELXTL 5.1.[28] Non-H atoms were refined with anisotropic displacement parameters. All hydrogen atoms, except for those on the hydroxy group, were constrained to parent sites, using a riding model. The high residuals in the final difference map are situated around 2.9 Å from Si20. Attempts to refine them as partially occupied solvent molecules failed. Full crystallographic data in CIF-format has been deposited (CCDC 617804). Crystal data: $C_{24}H_{35}O_4Si$, M=415.61, triclinic, a=6.608(4), b=8.91(2), c=19.75(2) Å, α=84.39(14), β=81.38(7), γ=77.90(13)°, V=1521.1(4) Å^3, space group $P1$, Z=2, D_{calcd}=1.231 g cm^{-3}, μ=0.132 mm^{-1} θ range=2.34–28.98°, 12957 reflections measured, 5017 unique (R_{int}=0.0948), which were used in all calculations. The final $wR(F^2)$ was 0.3086 (all data) and the $R(F)$ was 0.1222 ($I>2\sigma(I)$) using 264 parameters. S=1.493.

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Supplementary data

General experimental procedures. ^{1}H and ^{13}C NMR spectra for compounds **14** and **15** (isomeric mixture), **18**, **19**, **21** and **26**. COSY and NOESY spectra for the isomeric mixture of **14** and **15** and for compounds **27** and **28**. A figure giving atomic numbering of the DIAMOND drawing of compound **27**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.09.015.

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