An unexpected Prins desymmetrisation reaction driven by silyl migration

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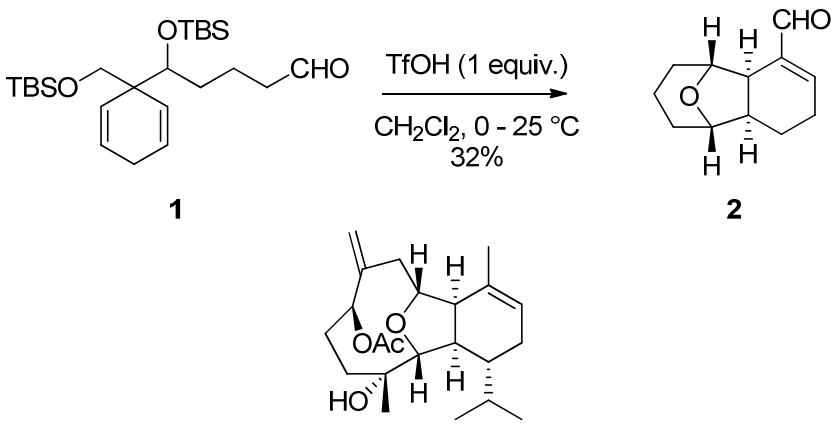
Dedicated to Professor Keith Smith on the occasion of his 65th birthday

Abstract
Prins desymmetrisation reactions of cyclohexa-1,4-diene derivatives have been investigated as a route to the core of the cladiellin diterpenes. During the course of this work, we observed the formation of a partially-reduced benzofuran **18**, which is clearly derived from oxocarbenium ion **21**. This can only be rationalised by an unexpected primary to secondary silyl group migration.

Keywords: Prins reaction, tetrahydrofuran, heterocycle, diterpene, natural product

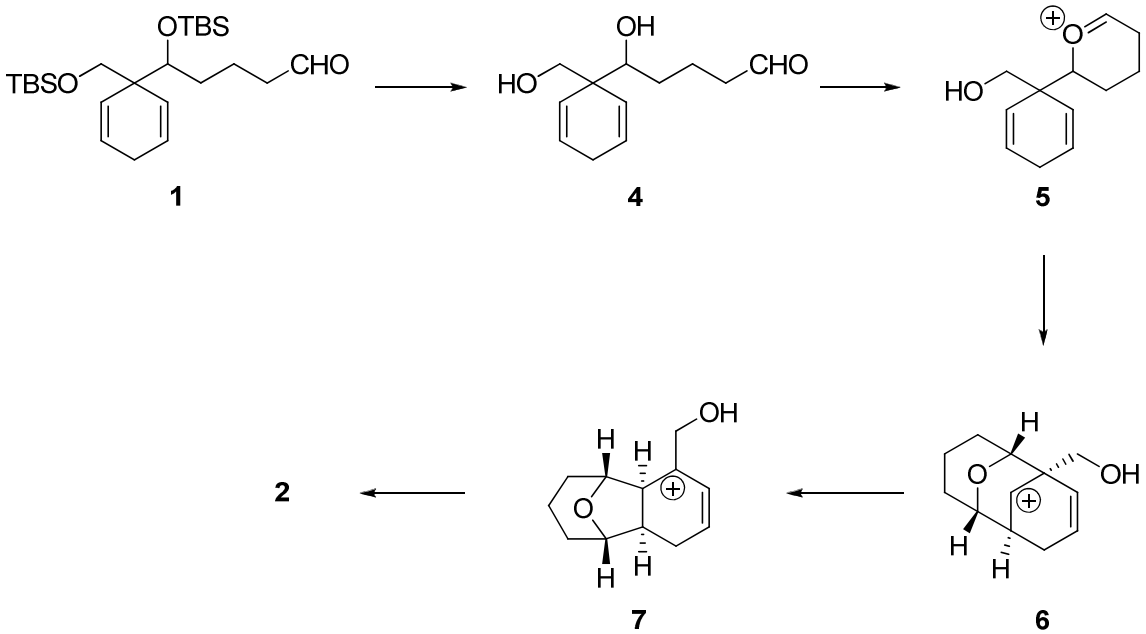
Introduction

We have recently reported model studies for the Prins desymmetrisation of cyclohexa-1,4-dienes to give systems related to the cladiellin diterpenes.[1] In our initial work, compound **1** underwent a rather dramatic transformation into compound **2** by way of formation and reaction of an oxocarbenium ion followed by rearrangement. In this way, the core functionality and stereochemistry of the cladiellin diterpenes, for example 7-deacetoxyalcyonin acetate (**3**)[2] was rapidly established (Scheme 1).



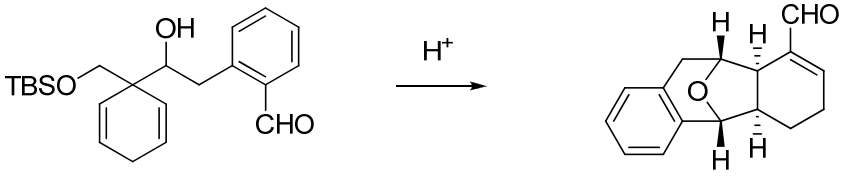
Scheme 1

This reaction involves the double-deprotection of compound **1** to give intermediate **4**, followed by formation of oxocarbenium ion **5**, cyclisation to give **6** which rearranges to give **7** and deprotonation/tautomerisation to give the product **2** (Scheme 2).



Scheme 2

In seeking to extend these studies, we elected to fuse an additional ring onto the precursor as shown in Scheme 3. While the fusion of an aromatic ring is appropriate for such a study, we envisage that eventually this will be replaced with a system that can be cleaved to give the complete cladiellin core. It was therefore envisaged that the Prins desymmetrisation of compound **8** would give rise to compound **9**.

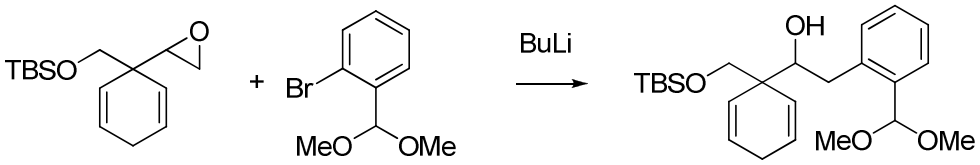


8 **9**

Scheme 3

Results and Discussion

It was envisaged that the key precursor **12** would be accessible by formation of an organolithium compound from **11** and then reaction with the epoxide **10** (Scheme 4).

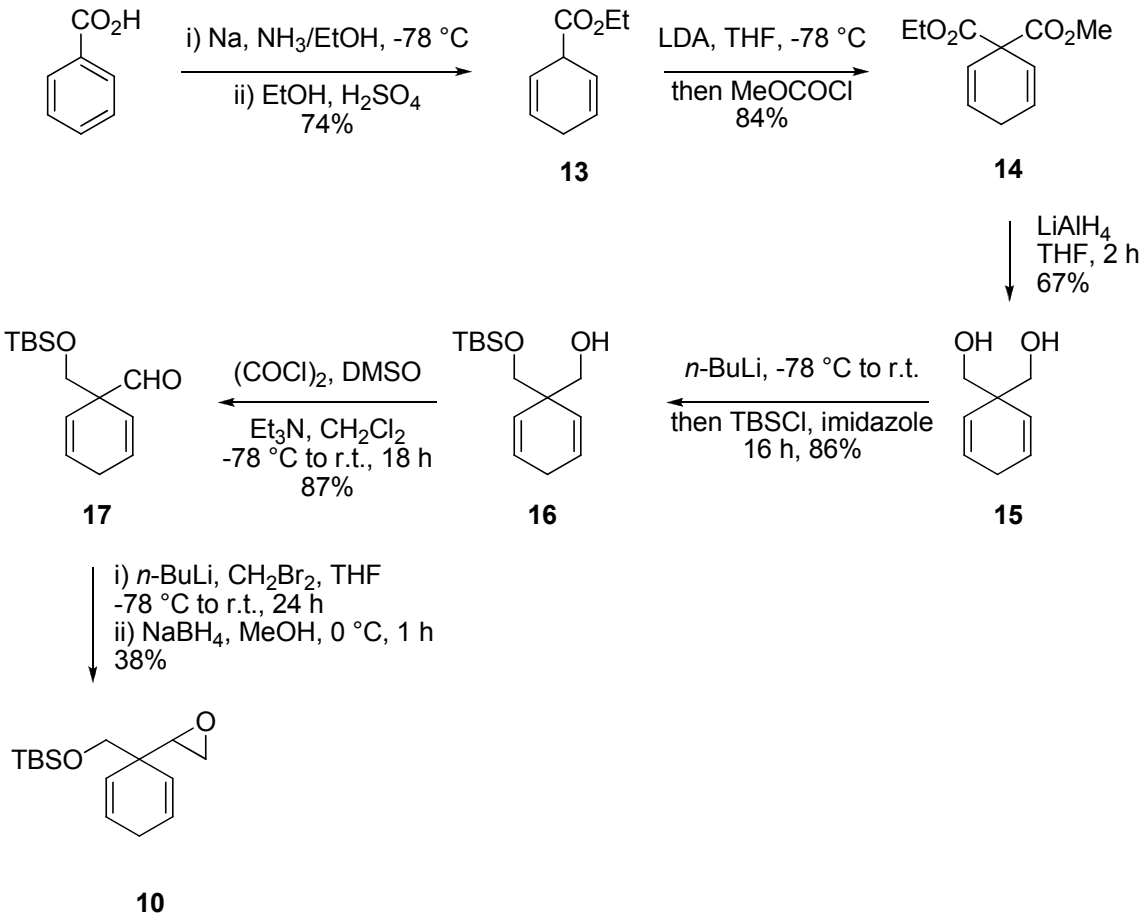


10 **11** **12**

Scheme 4

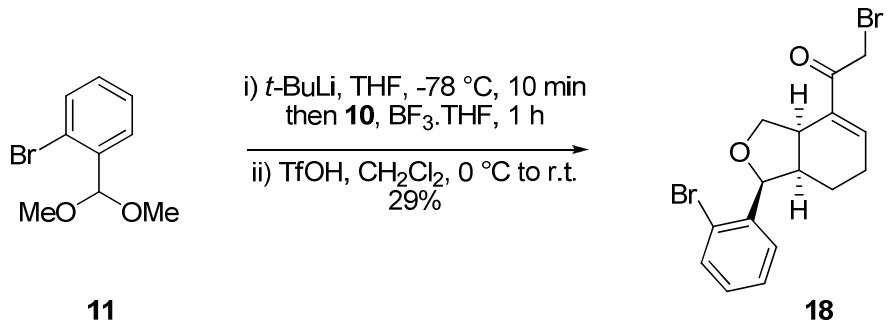
Compound **11** was prepared according to a literature method.[3] Compound **10** was prepared as shown in Scheme 5. Birch reduction of benzoic acid followed by esterification gave compound **13**. Deprotonation and acylation with methyl chloroformate was followed by lithium aluminium hydride reduction to give diol **15**. Mono-silylation and Swern oxidation then gave aldehyde **17**. Addition of bromomethyllithium to the aldehyde was rather troublesome. With an excess of bromomethyllithium complex mixtures of products were obtained. Therefore it was better to use only a slight excess. Under these conditions the reaction did not proceed to completion, but the unreacted aldehyde was readily removed by treatment of the crude reaction mixture with sodium borohydride prior to chromatography. This gave the desired epoxide **10** in satisfactory yield.

Lithiation of compound **11** with *t*-BuLi for 10 minutes at -78 °C prior to addition of epoxide **10** initially appeared to have been successful. Purification gave a product in which the acetal had been retained along with a 1,2-disubstituted benzene ring, and that the epoxide had been opened. This was therefore subjected to the conditions of the Prins desymmetrisation (Scheme 6). It rapidly became clear that the product of this two-step process was the partially-reduced benzofuran **18** rather than the desired product. The structural assignment of compound



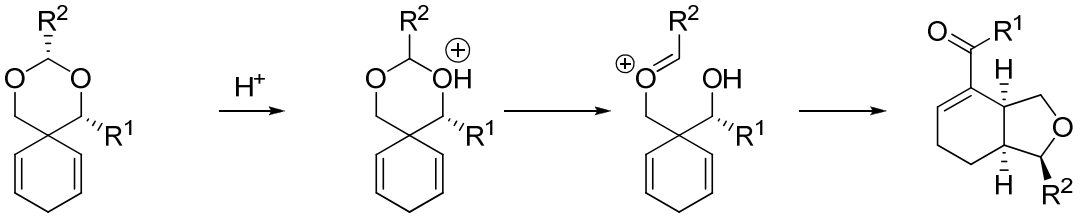
Scheme 5

18 was by no means straightforward. Extensive analysis of ^{1}H and ^{13}C NMR spectroscopic data, and ^{1}H–^{1}H and ^{1}H–^{13}C correlation data (COSY, HMBC and HSQC) enabled determination of the carbon-hydrogen framework connectivity. Mass spectrometric studies identified the presence of the two bromine atoms in the compound **18**. The stereochemistry of compound **18** was assigned by analogy with that of related compounds.[1b]



Scheme 6

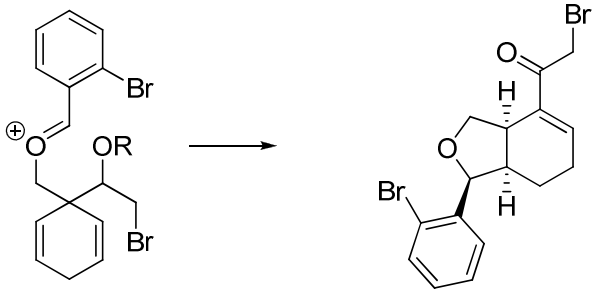
In a previous study, we reported the formation of ketones during Prins desymmetrisation reactions.[1b] These arise by protonation of an acetal **19** on the more hindered oxygen followed by the Prins reaction, and compounds **20** were invariably the minor products (Scheme 7). In this case compound **14** was the only product formed, which suggests that if an acetal such as **19** is formed, it is opened regioselectively but in the "wrong" direction. This seems rather unlikely.



19 **20**

Scheme 7

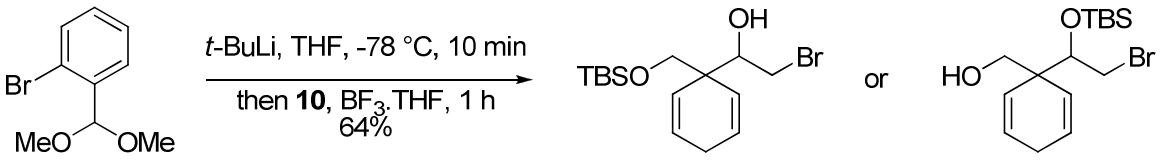
However, since the structure of compound **18** is secure, it is clear that it must be formed from oxocarbenium ion **21** (R = H or TBS). Since it is unlikely that opening of an acetal forms this intermediate, the most likely explanation is opening of epoxide **10** by bromide derived from the partial lithiation of compound **11**.



21 **18**

Scheme 8

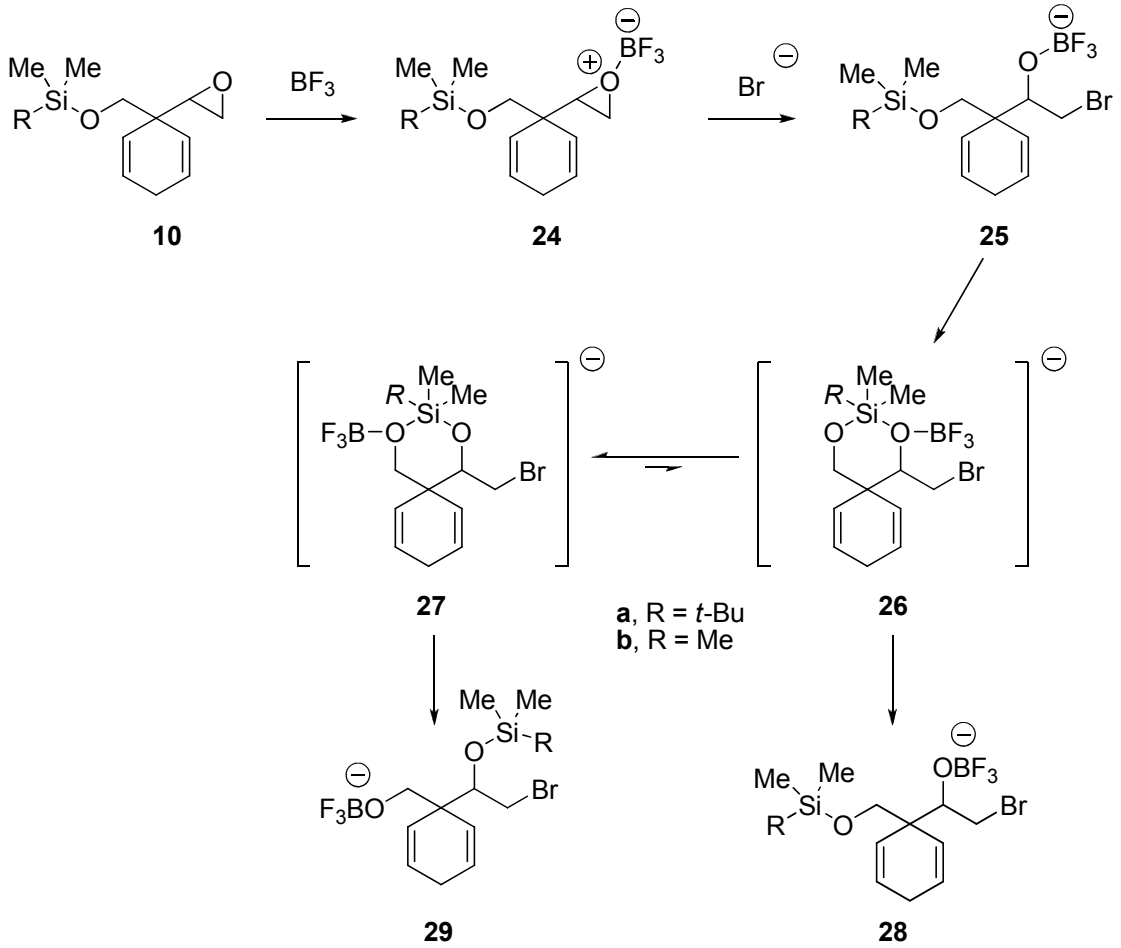
In order to investigate this process further, the coupling of compounds **10** and **11** was repeated. Extensive chromatography led to the isolation of an epoxide-opening product that lacked the aromatic ring (Scheme 9). This was assigned structure **22** or **23**, although we could not *a priori* deduce the location of the silyl group. Examination of the spectra from the previous coupling reaction showed that the same epoxide-opening product was present. As a result of the subsequent formation of compound **18**, it seems overwhelmingly likely that the structure is **23** and not **22**, so that a silyl migration has taken place during the epoxide-opening.



11 **22** **23**

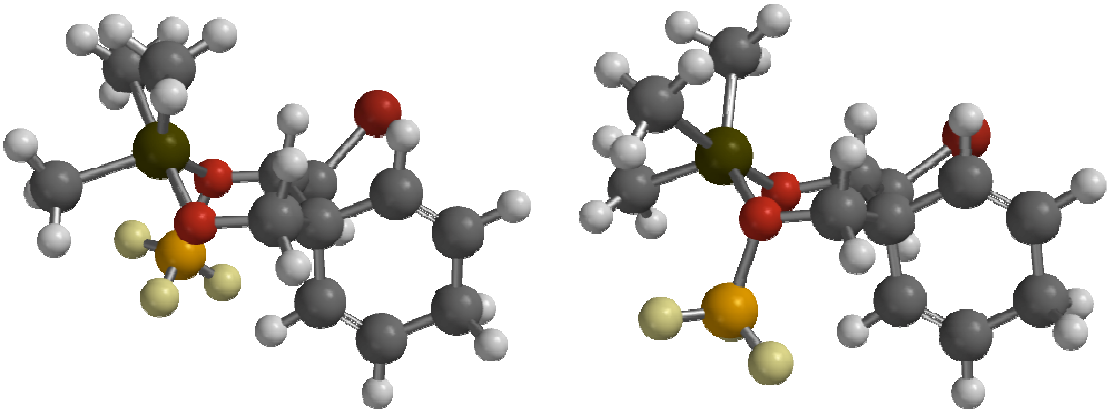
Scheme 9

Explaining this apparent silyl migration is not straightforward. While there are many examples of silyl groups migrating from secondary to primary alcohols in the literature,[4] we could find no examples of primary to secondary migration, and we assume that such a process would be kinetically disfavoured. However, if we assume that the BF_3 coordinates to the epoxide oxygen in order to assist the epoxide-opening, we can consider the intermediacy of a hypervalent silicon compound **26a** (Scheme 10). The BF_3 should then be readily transferred to the less-hindered oxygen which will give intermediate **27a** which should then undergo opening with effective silyl-transfer to give **29a**. In fact, this process is very reminiscent of the regioselective opening of the corresponding acetals with Lewis acids.[1]



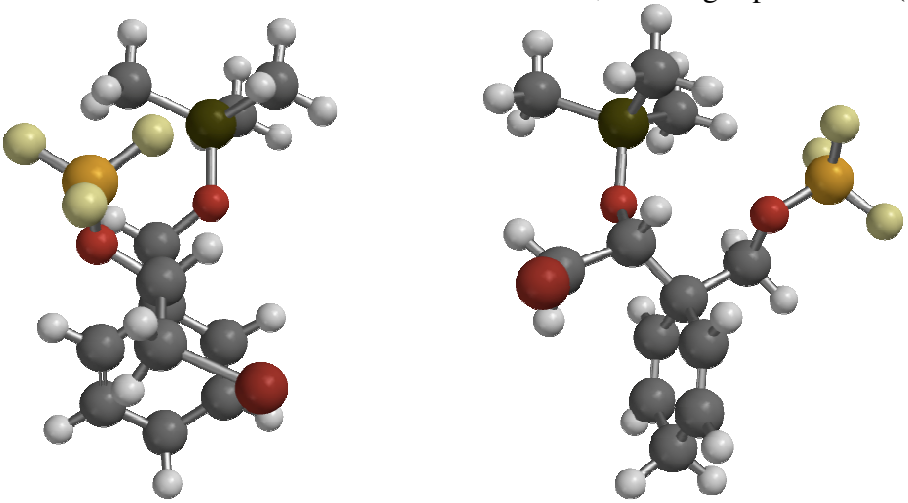
Scheme 10

Density functional theory calculations (Spartan 10, B3LYP 6-31+G*) have provided some insight into this transformation. For simplicity the calculations were carried out with a trimethylsilyl group in place of TBS. Both **26b** and **27b** minimise at this level of theory with cleavage of a Si-O bond, so that it was not possible to obtain minimum energy structures for these intermediates. However, a single-point DFT calculation based on a molecular mechanics minimised structure in each case indicated that **27b** is considerably more stable than **26b** (235 kJ mol^{-1}, although since these numbers are not based on optimised structures, they should be interpreted cautiously) (Figure 1). In both cases the BF_3 is axial to avoid severe steric interactions with the trimethylsilyl group. However, upon minimisation, the product **29b** is more stable than **28b** (by 11.6 kJ mol^{-1}). The lowest energy conformers of these two structures are shown in Figure 2. Therefore, we would tentatively attribute the formation of intermediate **29** as being due to rapid migration of the BF_3 to the less-hindered oxygen.



-3807.72667 H -3807.74829 H

Figure 1. Spartan MMFF minimised structures of **26b** and **27b**, and single-point DFT (6-31+G*) energies.

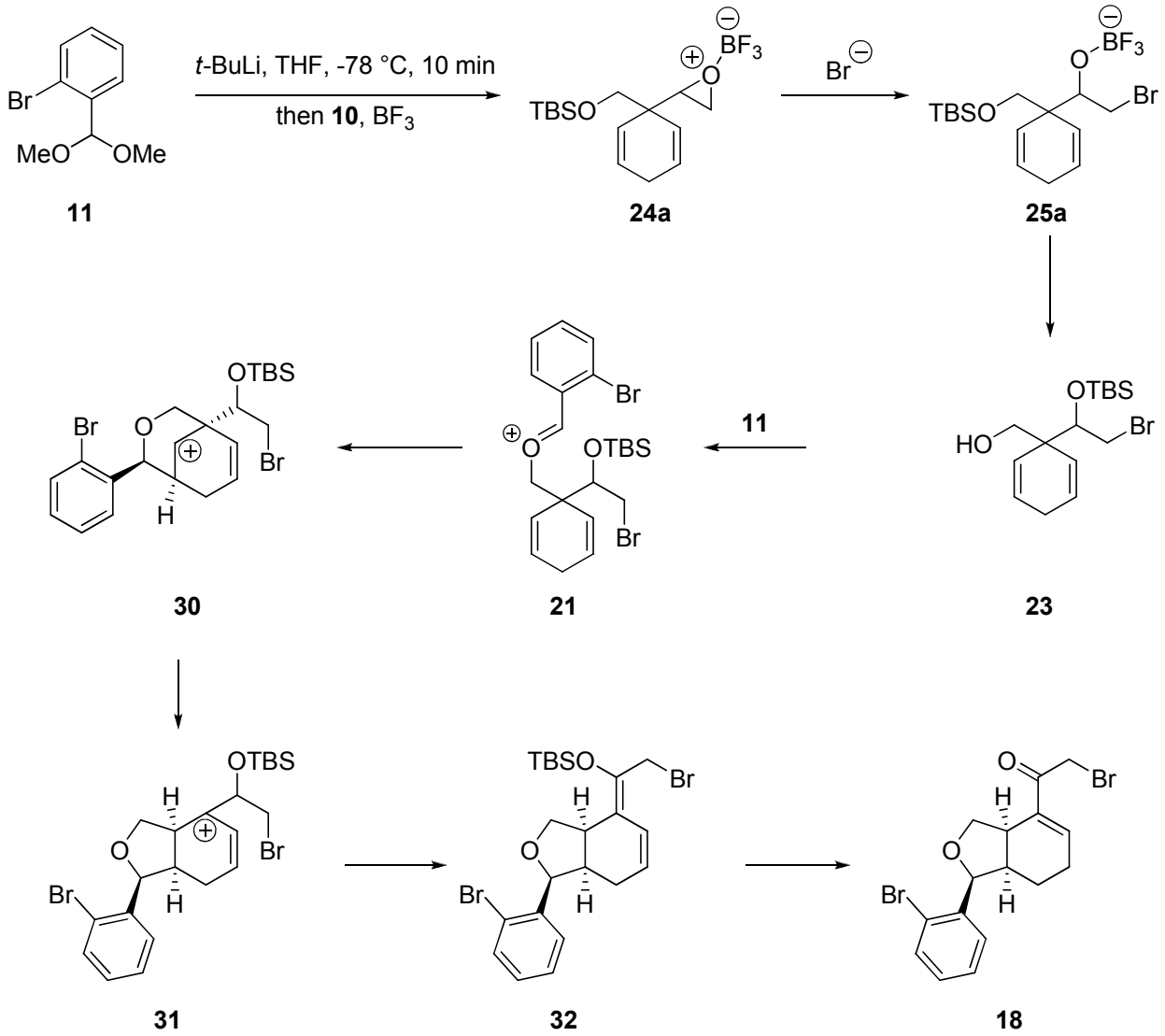


-3807.90925 H -3807.90484 H

Figure 2. B3LYP (6-31+G*) lowest energy conformers of **28b** and **29b**.

Conclusions

The formation of compound **18** was unanticipated on the basis of our previous work. However, it can be rationalised as a result of an unexpected primary to secondary silyl migration as follows. Metal-halogen exchange on compound **11** generates bromide. Presumably the organolithium reagent is also formed, but the fate of this species is unclear. Boron trifluoride promotes the opening of epoxide **10** with bromide to generate intermediate **25a**, which rearranges under the influence of the boron trifluoride to give the primary alcohol **23**. Oxocarbenium ion **21** is then formed by reaction with **11**, and cyclisation of this ion initially gives the secondary carbenium ion **30** before rearrangement to the more stable allylic carbenium ion **31**. Loss of a proton will be followed by hydrolysis and tautomerisation of the silyl enol ether **32** to ultimately give the observed product **18**.



Scheme 11

Experimental Section

General. Melting points were determined on a Gallenkamp melting point apparatus. Infrared spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded on a Fisons VG Platform II spectrometer and on a Micromass Q-TOF Micro spectrometer. NMR spectra were recorded on a Bruker DPX 400 spectrometer operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C at 25 °C, or on a Bruker Avance 500 spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C at 25 °C. All chemical shifts are reported in ppm downfield from TMS. Coupling constants (*J*) are reported in Hz. Multiplicity in ^{1}H NMR spectroscopy is reported as singlet (s), doublet (d), double doublet (dd), double triplet (dt), double quartet (dq), triplet (t), and multiplet (m). Multiplicity in ^{13}C NMR spectroscopy was obtained using the DEPT pulse sequence. Flash chromatography was performed using Matrex silica 60 35–70 micron. Solvents for moisture-sensitive reactions were dried by distillation; THF over sodium benzophenone ketal and CH_2Cl_2 over CaH_2. Such reactions were carried out under an atmosphere of nitrogen.

Ethyl cyclohexa-2,5-dienecarboxylate (**13**).[5] Sodium metal (6.22 g, 270 mmol) was added in portions to a solution of benzoic acid (10.0 g, 81.9 mmol) in liquid NH_3-EtOH (4:1, 500 ml) at -78 °C. After the blue colour had faded, solid NH_4Cl (17.5 g) was added and the ammonia was allowed to evaporate. The mixture was then acidified by addition of 2 M HCl and the aqueous layer extracted with Et_2O. The combined extracts were dried (Na_2SO_4) before the solvent was removed *in vacuo*. The residue was re-dissolved in EtOH (250 ml) and treated with conc. H_2SO_4 (~0.5 ml). The resulting solution was allowed to stir at room temperature for 16 h. The solvent was removed *in vacuo* and the reaction mixture neutralized by addition of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O and the combined extracts dried over Na_2SO_4. The solvent was removed *in vacuo* affording the title compound **13** (9.23 g, 74%) as a pure colourless oil. IR: ν_{max} (Nujol): 2981, 2873, 2821, 1735, 1366, 1179, 1034, 942 898, 715 and 668 cm^{-1}. NMR: δ_H (400 MHz; $CDCl_3$): 5.90 – 5.86 (2 H, m, alkene CH), 5.84 – 5.79 (2 H, m, alkene CH), 4.16 (2 H, q, J = 7.1, CH_2O), 3.75 – 3.68 (1 H, broad m, CH), 2.71 – 2.66 (2 H, broad m, CH_2) and 1.27 (3 H, t, J = 7.1, CH_3); δ_C (100 MHz; $CDCl_3$): 172.6 (C=O), 126.3 (2 × CH), 122.2 (2 × CH), 60.9 (CH_2), 41.7 (CH), 25.8 (CH_2) and 14.2 (CH_3).

1-Ethyl 1-methyl cyclohexa-2,5-diene-1,1-dicarboxylate (**14**). *n*-Butyllithium (13.2 ml of a 2.5 M solution in hexanes, 32.9 mmol) was added dropwise to a solution of diisopropylamine (4.61 ml, 32.9 mmol) in THF (50 ml) at 0 °C. The mixture was allowed to stir for 30 minutes at the same temperature before being cooled to -78 °C. The ester **13** (5.01 g, 33.0 mmol) was added dropwise and the reaction mixture allowed to stir for 30 minutes at -78 °C before methyl chloroformate (2.80 ml, 36.2 mmol) was added. The resulting solution was stirred for a further 15 minutes at -78 °C before the reaction was quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with Et_2O, the combined extracts being dried (Na_2SO_4) before the solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O: petroleum ether 1: 19)

afforded the title compound **14** (5.84 g, 84%) as a colourless oil. IR: ν_{max} (neat): 2984, 2956, 1735, 1436, 1251, 1205, 1064, 1038, 860, 801, 778 and 704 cm^{-1}. NMR: δ_H (400 MHz; $CDCl_3$): 6.07 – 6.02 (2 H, m, alkene CH), 5.98 (2 H, app. dt, *J* = 10.4, 1.8, alkene CH), 4.20 (2 H, q, *J* = 7.1, CH_2O), 3.75 (3 H, s, OCH_3), 2.72 – 2.70 (2 H, m, ring CH_2) and 1.26 (3 H, t, *J* = 7.1, CH_3); δ_C (100 MHz; $CDCl_3$): 170.3 (C), 169.6 (C), 127.8 (2 × CH), 122.2 (2 × CH), 61.9 (CH_2), 55.4 (C), 52.9 (CH_3), 25.9 (CH_2) and 14.0 (CH_3).

Cyclohexa-2,5-diene-1,1-diyldimethanol (**15**). A solution of diester **14** (5.84 g, 27.8 mmol) in THF (20 ml) was added slowly to a suspension of $LiAlH_4$ (2.11 g, 55.6 mmol) in THF (60 ml). The mixture was allowed to stir at room temperature for 2 h before being quenched by slow addition of aqueous 2 M NaOH solution. The solution was dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. Chromatography on silica gel (EtOAc: petroleum ether 2: 1) afforded the title compound **15** (2.59 g, 67%) as a colourless solid, m.p. 82 – 84 °C. IR: ν_{max} (Nujol): 3399, 2923, 2855, 1633, 1252, 1100, 1023, 984, 940, 898 and 707 cm^{-1}. NMR: δ_H (400 MHz; $CDCl_3$): 6.09 – 6.04 (2 H, m, alkene CH), 5.60 – 5.56 (2 H, m, alkene CH), 3.52 (4 H, s, 2 × CH_2O), 2.72 (2 H, app. tt, *J* = 3.4, 2.1, ring CH_2) and 1.69 (2 H, broad s, 2 × OH); δ_C (100 MHz; $CDCl_3$): 128.5 (2 × CH), 126.9 (2 × CH), 68.0 (2 × CH_2), 44.6 (C) and 26.9 (CH_2).

[1-[(*tert*-Butyldimethylsilyloxy)methyl]cyclohexa-2,5-dienyl]methanol (**16**). *n*-Butyllithium (2.40 ml of 2.5 M solution in hexanes, 6.01 mmol) was added to a solution of diol **15** (886 mg, 6.33 mmol) in THF (15 ml) at -78 °C. The resulting solution was allowed to warm to room temperature over 1 h before a solution of *tert*-butyldimethylsilyl chloride (859 mg, 5.70 mmol) in THF (5 ml) was added. The reaction mixture was stirred for 30 minutes before imidazole (cat.) was added. The resulting mixture was stirred for 16 h at room temperature before the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with Et_2O, the combined extracts being dried (Na_2SO_4) before the solvent was removed *in vacuo*. Chromatography on silica gel (EtOAc: petroleum ether 1: 1) afforded the title compound **16** (1.38 g, 86%) as a colourless oil. IR: ν_{max} (Neat): 3419, 3028, 2954, 2929, 2885, 2857, 1635, 1471, 1464, 1255, 1084, 1046, 940, 838, 776 and 708 cm^{-1}. NMR: δ_H (500 MHz; $CDCl_3$): 5.94 – 5.91 (2 H, m, alkene CH), 5.62 (2 H, app. dt, *J* = 10.5, 2.0, alkene CH), 3.59 (2 H, s, CH_2OTBS), 3.54 (2 H, s, C*H*$_2$OH), 2.70 – 2.68 (2 H, m, ring CH_2), 2.17 – 1.87 (1 H, broad s, OH), 0.89 (9 H, s, *t*-Bu) and 0.04 (6 H, s, 2 × CH_3); δ_C (125 MHz; $CDCl_3$): 127.3 (2 × CH), 127.0 (2 × CH), 69.7 (CH_2), 69.1 (CH_2), 43.6 (C), 27.1 (CH_2), 25.8 (3 × CH_3), 18.2 (C) and -5.6 (2 × CH_3). MS-APCI: *m/z* (%) = 255 ($M+H^+$, 100), 237 (21), 177 (17), 156 (7), 130 (6) and 105 (3). HRMS-APCI: *m/z* $[M + H]^+$ calcd for $C_{14}H_{27}O_2Si$: 255.1780; found: 255.1776.

1-[(*tert*-Butyldimethylsilyloxy)methyl]cyclohexa-2,5-dienecarbaldehyde (**17**).[6] Oxalyl chloride (0.59 ml, 6.89 mmol) was added dropwise into a solution of DMSO (1.12 ml, 15.7 mmol) in CH_2Cl_2 (20 ml) at -78 °C. The solution was stirred for 10 minutes before the alcohol **16** (499 mg, 1.96 mmol) was added dropwise. After stirring for a further 10 minutes at -78 °C, triethylamine (3.57 ml, 25.6 mmol) was added and the reaction mixture allowed to warm to room temperature over 2 h. The reaction was quenched by pouring into saturated aqueous $NaHCO_3$ solution. The crude product was extracted with CH_2Cl_2, the combined extracts being dried

(Na_2SO_4) before the solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O: petroleum ether 1: 49) afforded the title compound **17** (429 mg, 87%) as a colourless oil. IR: ν_{max} (Neat): 3032, 2955, 2929, 2886, 2857, 1729, 1651, 1634, 1471, 1420, 1256, 1111, 1083, 839, 778 and 704 cm^{-1}. δ_H (400 MHz; $CDCl_3$): 9.51 (1 H, s, aldehyde CH), 6.04 – 6.00 (2 H, m, alkene CH), 5.71 (2 H, app. dt, *J* = 10.5, 2.0, alkene CH), 3.76 (2 H, s, CH_2OTBS), 2.74 – 2.72 (2 H, m, ring CH_2), 0.86 (9 H, s, *t*-Bu) and 0.03 (6 H, s, 2 × CH_3). δ_C (100 MHz; $CDCl_3$): 200.9 (aldehyde CH), 128.3 (2 × CH), 122.7 (2 × CH), 67.3 (CH_2), 55.3 (C), 27.0 (CH_2), 25.7 (3 × CH_3), 18.2 (C) and -5.6 (2 × CH_3).

***tert*-Butyldimethyl[[1-(oxiran-2-yl)cyclohexa-2,5-dienyl]methoxy]silane** (**10**). *n*-Butyllithium (1.75 ml of a 2.5 M solution in hexanes, 4.37 mmol) was added to a solution of aldehyde **17** (1.00 g, 3.97 mmol) and dibromomethane (0.42 ml, 5.95 mmol) in THF (30 ml) at -78 °C. The reaction mixture was warmed to room temperature and stirred for 24 h, before being quenched with saturated aqueous NH_4Cl. The mixture was extracted with ether, the combined extracts being dried (Na_2SO_4) before the solvent was removed *in vacuo* affording a crude mixture of aldehyde and epoxide (aldehyde: epoxide ~ 2:7, 1.09 g). The aldehyde and epoxide were inseparable by column chromatography, so the crude mixture was re-dissolved in MeOH (15 ml) and $NaBH_4$ (75 mg, 1.98 mmol) added to reduce the excess aldehyde. After stirring for 1 h at room temperature, the reaction was quenched with water and the mixture extracted with ether, the combined extracts being dried (Na_2SO_4) before the solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O: petroleum ether 1:49) afforded the title compound **10** (400 mg, 38%) as a colourless oil. IR: ν_{max} (Neat): 2955, 2929, 2886, 2857, 1471, 1464, 1254, 1106, 1080, 840, 777 and 719 cm^{-1}. NMR δ_H (400 MHz; $CDCl_3$): 5.91 – 5.83 (2 H, m, alkene CH), 5.67 (1 H, app. dq, *J* = 10.1, 2.0, alkene CH), 5.37 (1 H, app. dq, *J* = 10.3, 2.0, alkene CH), 3.63 (1 H, d, *J* = 9.3, one of CH_2OTBS), 3.48 (1 H, d, *J* = 9.3, one of CH_2OTBS), 3.13 (1 H, dd, *J* = 4.0, 2.9, epoxide CH), 2.66 – 2.64 (3 H, m, one of epoxide CH_2 and ring CH_2), 2.60 (1 H, dd, *J* 5.1, 2.9, one of epoxide CH_2), 0.90 (9 H, s, *t*-Bu), 0.05 (3 H, s, CH_3) and 0.04 (3 H, s, CH_3); δ_C (100 MHz; $CDCl_3$): 127.6 (CH), 126.2 (CH), 126.1 (CH), 124.9 (CH), 68.6 (CH_2), 55.2 (CH), 44.3 (CH_2), 41.8 (C), 27.0 (CH_2), 25.8 (3 × CH_3), 18.3 (C) and -5.5 (2 × CH_3). MS-APCI: *m/z* (%) = 267 ($M+H^+$, 100), 249 (28), 176 (8), 156 (13), 132 (22) and 115 (3). HRMS-APCI: *m/z* [M + H]$^+$ calcd for $C_{15}H_{27}O_2Si$: 267.1780; found: 267.1771.

[1-[2-Bromo-1-(tert-butyldimethylsilyloxy)ethyl]cyclohexa-2,5-dienyl]methanol (**23**). *t*-Butyllithium (1.00 ml of 1.7 M solution in pentane, 1.70 mmol) was added to a solution of bromide **11** (196 mg, 0.850 mmol) in THF (10 ml) at -78 °C. After stirring for 10 minutes epoxide **10** (113 mg, 0.425 mmol) was added. The resulting solution was stirred for 15 minutes at -78 °C before BF_3.THF (0.05 ml, 0.425 mmol) was added. After stirring for an additional 1 h, the reaction was quenched at -78 °C with saturated aqueous NH_4Cl solution. The mixture was extracted with Et_2O, the combined extracts being dried (Na_2SO_4) before the solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O: hexane 1:99) afforded the title compound **23** (94 mg, 64%) as a colourless oil. IR: ν_{max} (Neat): 3478, 3029, 2928, 2857, 1472, 1253, 1106, 837, 777 and 655 cm^{-1}. NMR: δ_H (400 MHz; $CDCl_3$): 5.95 – 5.86 (2 H, m, alkene CH), 5.81 (1 H,

ddd, *J* = 10.4, 4.0, 2.0, alkene CH), 5.43 (1 H, ddd, *J* = 10.1, 4.1, 2.0, alkene CH), 4.01 (1 H, app. broad d, *J* = 10.5, CHOTBS), 3.72 (1 H, s, OH), 3.67 (1 H, d, *J* = 9.5, one of C*H*$_2$OH), 3.58 (1 H, d, *J* = 9.5, one of C*H*$_2$OH), 3.51 (1 H, dd, *J* = 10.5, 1.8, one of CH_2Br), 3.26 (1 H, t, *J* = 10.5, one of CH_2Br), 2.68 – 2.64 (2 H, m, ring CH_2), 0.89 (9 H, s, *t*-Bu) and 0.05 (6 H, s, 2 × CH_3); δ_C (100 MHz; $CDCl_3$): 127.4 (CH), 127.1 (CH), 126.6 (CH), 124.4 (CH), 76.5 (CH), 70.8 (CH_2), 45.2 (C), 37.9 (CH_2), 27.2 (CH_2), 25.8 (3 × CH_3), 18.2 (C) and -5.6 (2 × CH_3). MS-APCI: *m/z* (%) = 349 (100), 347 (M+H$^+$, 94), 331 (27), 329 (24), 217 (53), 215 (50), 199 (34), 197 (35), 158 (6), 156 (13), 132 (18) and 117 (12). HRMS-APCI**:** *m/z* [M + H]$^+$ calcd for $C_{15}H_{28}{}^{79}BrO_2Si$: 347.1042; found: 347.1030.

2-Bromo-1-[(1*RS*,3a*SR*,7a*SR*)-1-(2-bromophenyl)-1,3,3a,6,7,7a-hexahydroisobenzofuran-4-yl]ethanone (**18**). *t*-Butyllithium (1.33 ml of 1.7 M solution in pentane, 2.26 mmol) was added to a solution of bromide **11** (261 mg, 1.13 mmol) in THF (10 ml) at -78 °C. After stirring for 10 minutes epoxide **10** (155 mg, 0.58 mmol) was added. The resulting solution was stirred for 15 minutes at -78 °C before BF_3.THF (0.07 ml, 0.56 mmol) was added. After stirring for an additional 1 h, the reaction was quenched at -78 °C with saturated aqueous NH_4Cl solution. The mixture was extracted with Et_2O, the combined extracts being dried (Na_2SO_4) before the solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O: hexane 1:99) afforded an approximately 1:1 mixture of bromide **11** and compound **23** (157 mg) as a colourless oil. Trifluoromethanesulfonic acid (0.01 ml, 0.12 mmol) was added to a sample of the mixture of compounds **11** and **23** (51 mg) in CH_2Cl_2 (2 ml) at 0 °C. The resulting solution was warmed to room temperature and stirred for 15 minutes before a further portion of trifluoromethanesulfonic acid (0.01 ml, 0.12 mmol) was added. After stirring for an additional 10 minutes, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution. The crude mixture was extracted with CH_2Cl_2, the combined extracts being dried (Na_2SO_4) before the solvent was removed *in vacuo*. Chromatography on silica gel (Et_2O: hexane 1:9) afforded the title compound **18** (22 mg, 29%) as a colourless oil. NMR: δ_H (400 MHz; $CDCl_3$): 7.56 – 7.51 (2 H, m, aryl CH), 7.30 (1 H, app. td, *J* = 7.6, 1.0, aryl CH), 7.13 (1 H, app. td, *J* = 7.6, 1.6, aryl CH), 7.07 (1 H, app. dd, *J* = 5.3, 1.7, alkene CH), 5.31 (1 H, d, *J* = 4.8, CHO), 4.50 (1 H, dd, *J* = 9.2, 8.2, one of CH_2O), 4.19 (2 H, s, CH_2Br), 3.63 (1 H, app. dd, *J* = 9.0, 8.3, one of CH_2O), 3.49 – 3.41 (1 H, m, ring junction CH), 2.80 (1 H, ddt, *J* = 13.2, 6.6, 4.8, ring junction CH), 2.32 (1 H, dtd, *J* = 19.7, 5.4, 2.0, one of allylic CH_2), 2.24 – 2.14 (1 H, broad m, one of allylic CH_2), 1.08 (1 H, app, ddd, *J* = 24.9, 13.2, 5.2, one of CH_2) and 0.90 – 0.82 (1 H, m, one of CH_2); δ_C (100 MHz; $CDCl_3$): 192.1 (C=O), 143.6 (alkene CH), 138.7 (C), 137.3 (C), 132.3 (CH), 128.6 (CH), 128.2 (CH), 127.0 (CH), 121.3 (C), 82.8 (CH), 72.0 (CH_2), 38.4 (CH), 38.3 (CH), 29.7 (CH_2), 25.8 (CH_2) and 19.2 (CH_2). MS-APCI: *m/z* (%) = 403 (48), 401 (100), 399 (M+H$^+$, 52), 385 (33), 383 (65), 381 (34) and 219 (34). HRMS-APCI: *m/z* [M + 1]$^+$ calcd for $C_{16}H_{17}{}^{79}Br_2O_2$: 398.9595; found: 398.9585.

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