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Synthesis of a 4,5-epoxy-2-cyclohexen-1-one derivative *via* epoxide ring opening, 1,3-carbonyl transposition and epoxide ring regeneration: a synthetic study on a scyphostatin analogue

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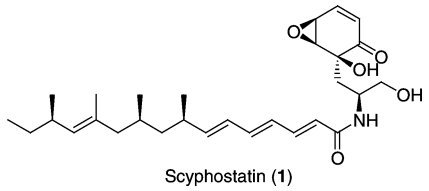
A 6-alkyl-4,5-epoxy-6-hydroxy-2-cyclohexen-1-one derivative, a model compound for the hydrophilic moiety of scyphostatin, was stereoselectively synthesized from the Diels–Alder adduct. The key steps were the reductive cleavage of the 4,5-epoxide ring of the epoxidated adduct, the 1,3-carbonyl transposition of the 3-carbonyl group to the C1 position by a Wharton reaction and stereoselective bromination to provide a *trans* bromohydrin derivative, a precursor to the desired compound. Desilylation of the bromohydrin derivative with TBAF directly gave the target compound.

Introduction

There are many natural products with highly functionalized cyclohexane moieties that exhibit prominent biological activities and many synthetic studies on such molecules have been reported (*e.g.* epoxyquinol,[1] nisamycis,[2] aranorosin[3] and epoxysorbicillinol[4]). Scyphostatin **1** also consists of a hydrophilic 6-alkyl-4,5-epoxy-6-hydroxy-2-cyclohexen-1-one moiety (Fig. 1).[5] Several synthetic approaches toward scyphostatin **1** have been reported[6] and a total synthesis has recently been achieved by Katoh *et al.*[7] We have also been interested in this natural product[8] and, through studies aimed at the total synthesis of this compound, we found that in the Diels–Alder reaction of 2,5-cyclohexadien-1-one bearing a spirolactone moiety with cyclopentadiene high π-facial selectivity is observed even when steric hindrance is not in play.[8a,b] Based upon this finding, we developed an efficient method for the synthesis of a 4,5-epoxy-2-cyclohexene-1-one derivative, as an analogue of the hydrophilic moiety (lacking the chiral amine moiety) of scyphostatin **1**, from the Diels–Alder adduct (Fig. 2).[8c–e]



Scyphostatin (**1**)

Fig. 1

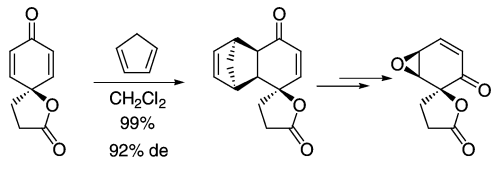
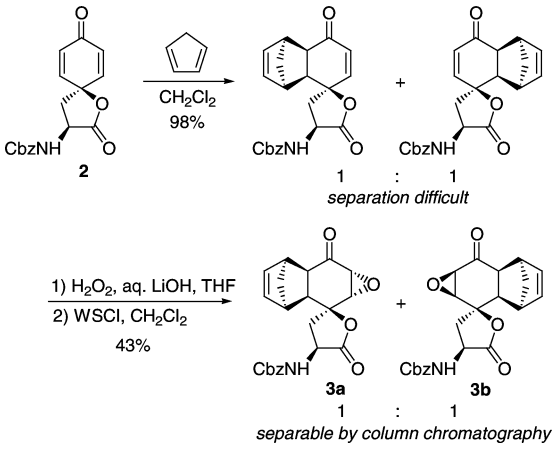
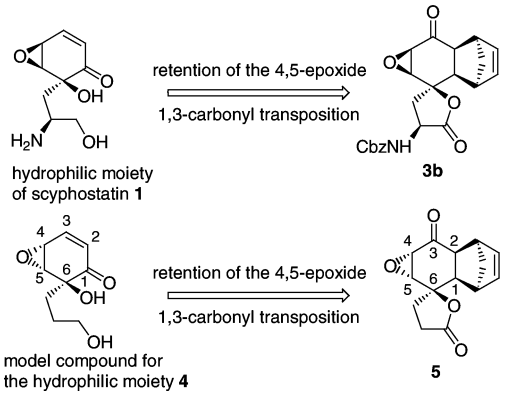


Fig. 2

Application of the developed procedure to spirolactone **2**, which bears the required amine moiety with the correct stereochemistry, followed by epoxidation gave rise to an unbiased 1 : 1 mixture of *exo*-epoxide **3a** and *endo*-epoxide **3b** (Scheme 1).[9] Epoxide **3a** has been found to be a suitable intermediate for a precursor to the hydrophilic moiety of scyphostatin.[8c,e] In order to utilize *endo*-epoxide **3b**, which incidentally has the required epoxide absolute stereochemistry for the hydrophilic moiety of scyphostatin **1**, a synthetic protocol involving the overall retention of the 4,5-epoxide ring and a 1,3-carbonyl transposition[10] are necessary (Scheme 2). We selected readily available spirolactone **5**[8c,e,11] as a model compound for **3b** to examine these two synthetic issues. Although the relative stereochemistry between the epoxide and the hydroxyl group on the ring in **5** is not the same as that in epoxide **3b**, we considered the model system sufficiently informative since this stereochemical difference is not relevant to our two objectives. In this paper, a successful conversion of **5** to an ester of **4**, a model of the hydrophilic moiety of scyphostatin **1**, is described.



Scheme 1



Scheme 2

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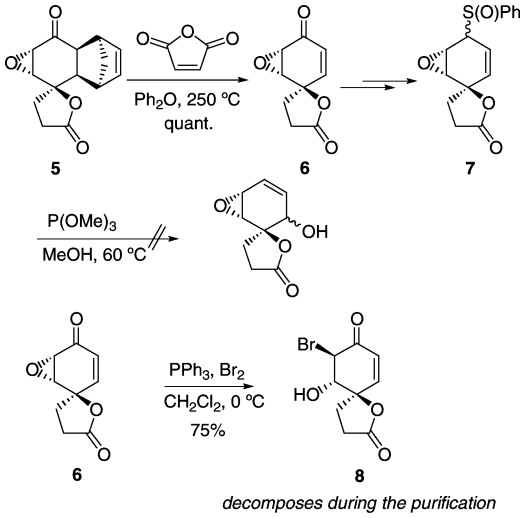
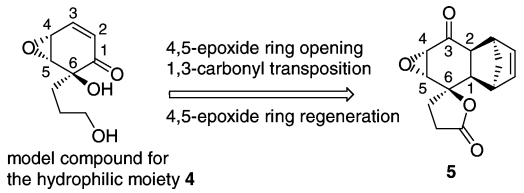
Results and disccusion

First, we investigated procedures in which the 4,5-epoxide ring of **5** is retained (Scheme 3). The retro-Diels–Alder product **6**[8e] was converted to sulfoxide **7** in order to attempt a sulfoxide–sulfenate rearrangement.[12] Heating sulfoxide **7** in the presence of $P(OMe)_3$ gave a complex mixture. 1,3-Carbonyl transposition by Asaoka's procudure[10c,e] also failed: the retro-Diels–Alder product **6** was treated with PhSH in the presence of Et_3N. However, the desired 1,4-addition product was not obtained and the signal of the 4,5-epoxide ring disappeared in ^1H NMR of the crude product. Cleavage of the epoxide ring to a bromohydrin, which retains the stereochemical identity of the epoxide ring, was next examined. Treatment of the spirolactone **6** with PPh_3 and Br_2 gave **8**. But, the bromohydrin **8** was not stable enough for further reactions.

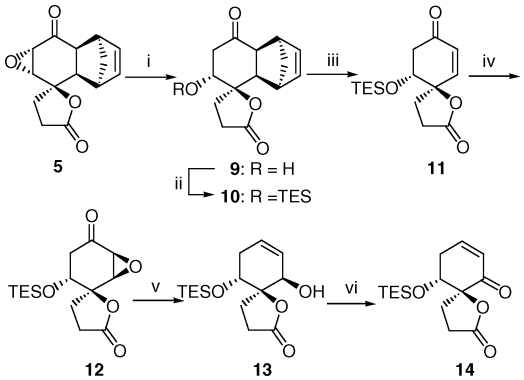


Scheme 3

As a second strategy, we planned a path involving the reductive cleavage of the 4,5-epoxide ring to an alcohol, 1,3-carbonyl transposition and regeneration of the 4,5-epoxide ring at the last stage (Scheme 4 and Scheme 5). By applying the method used in our previous work,[8c,e] the 4,5-epoxide ring of **5** was reductively cleaved with SmI_2 in 94% yield. The alcohol **9** was protected



Scheme 4



Scheme 5 *Reagents and conditions*: (i) SmI_2, MeOH, THF, −78 °C (94%); (ii) TESCl, imidazole, CH_2Cl_2, rt (98%); (iii) maleic anhydride, Ph_2O, 230 °C (99%); (iv) H_2O_2, aq. LiOH, THF, 0 °C (88%); (v) $NH_2NH_2{\cdot}H_2O$, AcOH, MeOH, rt (59%); (vi) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 °C (88%).

with a triethylsilyl group (TES) to give **10**, and **11** was obtained by the retro-Diels–Alder reaction of **10** (97%, two steps). The 1,3-carbonyl transposition was achieved by epoxidation of **11** with H_2O_2–LiOH, followed by Wharton reaction[13] (52%, two steps). The relative stereochemistry of the epoxide **12** was determined by ^1H NMR NOE experiments (Fig. 3). NOE enhancement between H1 and H1′ was observed. The observed facial selectivity in the epoxidation reaction can be attributed to attack on the face opposite to the lactone CH_2 group to avoid repulsion. In the Wharton reaction, a short reaction time was necessary to prevent over-reaction. The α,β-unsaturated ketone moiety was constructed by the Swern oxidation of **13** (88%).

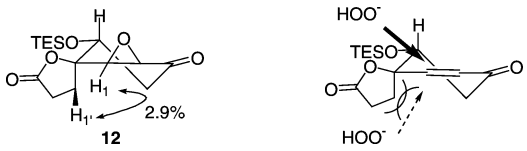
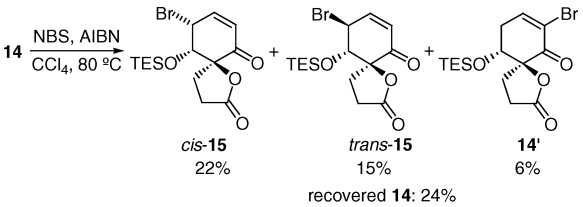


Fig. 3 Determination of the relative stereochemistry of **12** and stereoselectivity in the epoxidation of **11**.

For the introduction of a leaving group to regenerate the 4,5-epoxide ring, bromination of **14** with *N*-bromosuccinimide (NBS) was performed (Scheme 6). Treatment of **14** with NBS and a catalytic amount of 2,2′-azobis(isobutyronitrile) (AIBN) in CCl_4 at 80 °C for 2.5 h gave a mixture of *cis*- and *trans*-**15**, **14′** and recovered starting material (*cis*-**15**: 22%, *trans*-**15**: 15%, **14′**: 6%, recovered **14**: 24%). The relative stereochemistry of *cis*- and *trans*-**15** was determined by ^1H NMR NOE experiments and coupling constants ($^3J_{H4,H5}$) (Fig. 4). Prolonged reaction time prompted decomposition of **15**, resulting in a decrease in yield. Several other attempts (allylic oxidation with $Pd(OAc)_2$–*t*BuOOH–K_2CO_3[14] or SeO_2, bromination with *t*BuOK and NBS,[15] enolization of **11**, **12** and **14** with chlorotrimethylsilane and Et_3N) for the introduction of a leaving group at the C4 position also failed.



Scheme 6 Bromination of **14** with NBS.

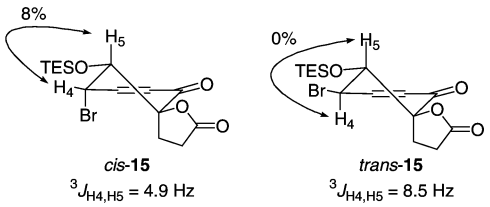
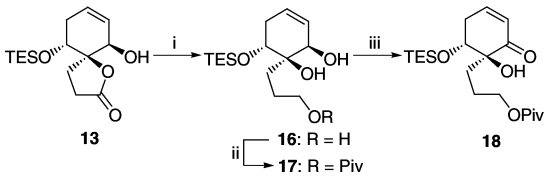


Fig. 4

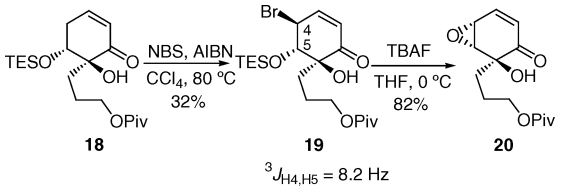
In order to improve the stereoselectivity in the bromination, the lactone ring of **13** was reduced to the alcohol by $LiAlH_4$ in 87% yield (Scheme 7). The alcohol **16** that formed was protected with a 2,2-dimethylpropionyl (Piv) group (89%).



Scheme 7 *Reagents and conditions*: (i) $LiAlH_4$, Et_2O, 0 °C (87%); (ii) PivCl, pyridine, 0 °C to rt (89%); (iii) IBX, DMSO, rt (92%).

Swern oxidation of **17** did not proceed. Treatment of **17** with MnO_2 gave a product generated by oxidative 1,2-diol cleavage. Oxidation of **17** with 2-iodoxybenzoic acid (IBX) was successful, affording α,β-unsaturated ketone **18** (92%).[16]

With α,β-unsaturated ketone **18** in hand, bromination with NBS was examined (Scheme 8).[17] Treatment of **18** with NBS in the presence of AIBN gave *trans*-bromide **19** (32%) as a single isomer with recovered **18** (42%). The relative stereochemistry was determined by the coupling constant $^3J_{H4,H5}$. Although bromide **19** was unstable under the reaction conditions, as was **15**, the stereoselectivity in the bromination reaction was improved. When **19** was treated with tetrabutylammonium fluoride (TBAF), 4,5-epoxy-2-cyclohexen-1-one **20** was obtained with spontaneous epoxide ring regeneration (82%).



Scheme 8 Bromination of **18** and regeneration of the 4,5-epoxide ring.

In order to rationalize the difference between the selectivities in the bromination of **14** and **18** with NBS (Fig. 5), PM3 calculations of the transition states leading to the products were performed using model compounds **21** and **23**.[18] Calculated heats of formation for the transition states leading to **22** indicate that *trans* attack is more favourable for conformation A whereas the opposite *cis* preference is likely for conformation B, with the difference in energy between these two favourable transition states being very small and the *cis* transition state having a slight edge. This is in good accord with the actual reaction of **14** slightly favouring the *cis* product. On the other hand, the two most favourable transition states for the reaction leading to **24** turn out to be those arising from *trans* attack for both ring conformations, with *cis* attack upon conformation **D** coming in third place. This may account for the high preference for *trans* attack in the reaction of **18**.

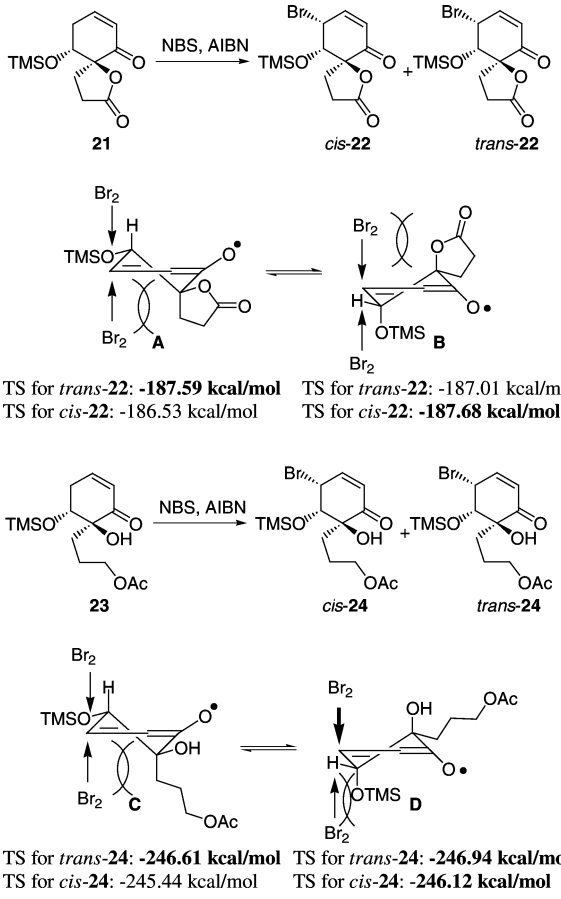


Fig. 5 PM3 calculations for the transition state in the bromination of **22** and **23**.

Conclusion

In summary, we have developed an efficient method for the synthesis of a 4,5-epoxy-2-cyclohexen-1-one derivative from **5**, which involves formal overall retention of the epoxide moiety and 1,3-carbonyl transposition. Since the 4,5-epoxide ring of **5** could not resist reaction conditions aimed to transform other parts of the cyclohexane ring, the 4,5-epoxide ring was reductively cleaved with SmI_2 and after several conversions, including the key 1,3-carbonyl transposition achieved by the Wharton reaction of **12**, the 4,5-epoxide ring was regenerated in the final step. High stereoselectivites were observed in the epoxidation of **11** and the bromination of **18**. The protocol developed here is currently being exploited in the actual synthetic system involving **3b**.

Experimental

All reactions were carried out under N_2. THF was distilled after refluxing over Na-benzophenone prior to use. CH_2Cl_2 was distilled over CaH_2 before use. Silica gel $60F_{254}$ (MERCK) was used for preparative thin layer chromatography (PTLC). NMR spectra were recorded on a JEOL JNM-LA500 instrument. The internal reference for ^1H NMR spectra was Me_4Si (TMS) (0.0 ppm) for $CDCl_3$. Chemical shifts for ^{13}C NMR spectra were referenced to $CDCl_3$ (77.0 ppm). MS spectra were recorded on a JEOL JMS-SX102A instrument. EI data were obtained by using 70 eV electrons. FAB spectra were measured by using glycerol as the matrix. Melting points were measured with a YANACO melting point apparatus. IR spectra were recorded on a HORIBA FT-IR720. Elemental analyses were carried out on a Perkin-Elmer 2400II analyzer.

6,7-Epoxy-10-triethylsilyloxy-1-oxaspiro[4.5]decane-2,8-dione (12)

A solution of 30% H_2O_2 (190.5 mg, 1.68 mmol) and 0.5 N LiOH (0.33 cm^3, 0.17 mmol) was added to a solution of **11**[8e] (86.9 mg, 0.29 mmol) in THF (3.0 cm^3) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. After diluting with aq. $Na_2S_2O_3$ and aq. NH_4Cl, the mixture was extracted with EtOAc. The combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, hexane–EtOAc 2 : 1) to give **12** (80.8 mg, 88%) as a white crystal: R_f (hexane–EtOAc 2 : 1) 0.3; mp 61–62 °C; ν(thin layer)/cm^{-1} 2951, 1772, 1733, 1377; δ_H (500 MHz, $CDCl_3$) 0.61 (6 H, q, *J* 7.9, –SiCH_2CH$_3$), 0.95 (9 H, t, *J* 7.9, –SiCH$_2$CH_3), 1.99 (1 H, ddd, *J* 9.2, 10.8 and 13.2, H4), 2.29 (1 H, dd, *J* 9.1 and 19.2, H9), 2.37 (1 H, ddd, *J* 3.6, 10.7 and 13.2, H4), 2.57 (1 H, ddd, *J* 3.6, 10.8 and 18.8, H3), 2.72 (1 H, ddd, *J* 9.2, 10.7 and 18.8, H3), 2.82 (1 H, dd, *J* 7.6 and 19.2, H9), 3.44 (1 H, d, *J* 4.0, H7), 3.62 (1 H, d, *J* 4.0, H6), 4.49 (1 H, dd, *J* 7.6 and 9.2, H10); δ_C (125 MHz, $CDCl_3$) 4.6 (–SiCH$_2$CH$_3$, × 3), 6.6 (–SiCH$_2$CH_3, × 3), 23.5 (C4), 28.9 (C3), 43.6 (C9), 55.6 (C7), 58.8 (C6), 66.5 (C10), 85.7 (C5), 176.0 (CO_2), 201.4 (CO); HRMS (EI) calcd for $C_{15}H_{24}O_5Si$ [M^+] 312.1393. Found 312.1404; anal. calcd for $C_{15}H_{24}O_5Si$: C, 57.66; H, 7.74%. Found: C, 57.60; H, 7.68%.

6-Hydroxy-10-triethylsilyloxy-1-oxaspiro[4.5]dec-7-en-2-one (13)

To a solution of **12** (571.8 mg, 1.83 mmol) in MeOH (90 cm^3) at rt was added dropwise $NH_2NH_2{\cdot}H_2O$ (0.18 cm^3, 3.7 mmol) and AcOH (0.21 cm^3, 3.7 mmol). The reaction mixture was stirred at rt for 10 min. After diluting with sat. $NaHCO_3$ and sat. NH_4Cl, the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The resulting residue was purified by column chromatography (silica gel, hexane–EtOAc 3 : 1) to give **13** (319.5 mg, 59%) as a colourless oil: R_f (hexane–EtOAc 1 : 1) 0.43; ν(thin film)/cm^{-1} 3430, 2954, 2911, 1778, 1239, 1217; δ_H (500 MHz, $CDCl_3$) 0.61 (6 H, q, *J* 8.2, –SiCH_2CH$_3$), 0.94 (9 H, t, *J* 8.2, –SiCH$_2$CH_3), 1.75 (1 H, ddd, *J* 7.9, 10.7 and 13.1, H4), 2.14 (1 H, ddd, *J* 2.6, 7.8 and 18.5, H9), 2.36 (1 H, ddd, *J* 4.9, 10.7 and 13.1, H4), 2.53–2.62 (3 H, m, OH, H3, H9), 2.69 (1 H, ddd, *J* 7.9, 10.7 and 18.0, H3), 4.15 (1 H, d, *J* 4.9, H6), 4.36 (1 H, dd, *J* 6.1 and 7.8, H10), 5.71–5.76 (1 H, m, H7), 5.80 (1 H, ddd, *J* 2.6, 4.1 and 9.9, H8); δ_C (125 MHz, $CDCl_3$) 4.8 (–Si*C*H$_2$CH$_3$, × 3), 6.7 (–SiCH$_2$*C*H$_3$, × 3), 24.4 (C4), 29.4 (C3), 34.2 (C9), 67.6 (C10), 71.8 (C6), 88.7 (C5), 125.1 (C7), 129.8 (C8), 176.8 (CO_2); HRMS (EI) calcd for $C_{15}H_{26}O_4Si$ [M^+] 298.1600. Found 298.1594; anal. calcd for $C_{15}H_{26}O_4Si$: C, 60.37; H, 8.78%. Found: C, 60.47; H, 8.86%.

10-Triethylsilyloxy-1-oxaspiro[4.5]dec-7-ene-2,6-dione (14)

A solution of $(COCl)_2$ (0.27 cm^3, 3.1 mmol) and DMSO (0.29 cm^3, 4.1 mmol) in CH_2Cl_2 (2.5 cm^3) was stirred at −78 °C for 40 min, followed by addition of a solution of **13** (319.3 mg, 1.07 mmol) in CH_2Cl_2 (2.5 cm^3). The reaction mixture was stirred at −78 °C for 30 min. After addition of Et_3N (1.26 cm^3, 9.05 mmol), the reaction mixture was stirred at −78 °C for 45 min. After diluting with sat. NH_4Cl, the mixture was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel, hexane–EtOAc 2 : 1) to give **14** (261.5 mg, 88%) as a colourless oil: R_f (hexane–EtOAc 1 : 1) 0.5; δ_H (500 MHz, $CDCl_3$) 0.64 (6 H, q, *J* 7.6, –SiCH_2CH$_3$), 0.96 (9 H, t, *J* 7.6, –SiCH$_2$CH_3), 1.90 (1 H, ddd, *J* 3.6, 8.9 and 12.7, H4), 2.44–2.78 (5 H, m, H3, H4, H9 × 2), 4.35 (1 H, dd, *J* 5.8 and 9.4, H10), 6.10 (1 H, dd, *J* 2.7 and 10.1, H8), 6.92 (1 H, ddd, *J* 2.1, 6.1 and 10.1, H7); δ_C (125 MHz, $CDCl_3$) 4.7 (–Si*C*H$_2$CH$_3$, × 3), 6.7 (–SiCH$_2$*C*H$_3$, × 3), 22.4 (C4), 27.6 (C3), 33.8 (C9), 70.0 (C10), 89.1 (C5), 127.7 (C7), 147.3 (C8), 176.9 (CO_2), 195.4 (CO); HRMS (EI) calcd for $C_{15}H_{24}O_4Si$ [M^+] 296.1444. Found 296.1456.

9-Bromo-10-triethylsilyloxy-1-oxaspiro[4.5]dec-7-ene-2,6-dione (15)

To a solution of **14** (36.2 mg, 0.122 mmol) in CCl_4 (0.6 cm^3) was added recrystallized NBS (13.0 mg, 0.073 mmol) and AIBN (0.7 mg, 0.004 mmol). The reaction mixture was heated at 80 °C. After 1.5 h, a solution of NBS (13.0 mg, 0.073 mmol) and AIBN (0.4 mg, 2 mmol) in CCl_4 (0.3 cm^3) was added to the reaction mixture. The reaction mixture was heated at 80 °C for 45 min, cooled and diluted with CCl_4. The precipitate that formed was filtered and the filtrate was evaporated. The residue was purified by preparative TLC (silica gel, hexane–EtOAc 2 : 1) to give *cis*- and *trans*-**15**, brominated compound **14′** and recovered **14** (*cis*-**15**: 10.7 mg, 22%, *trans*-**15**: 6.3 mg, 15%, **14′**: 2.6 mg, 6%, **14**: 8.5 mg, 24%). *cis*-**15**: colourless oil; R_f (hexane–EtOAc 1 : 1) 0.7; δ_H (500 MHz, $CDCl_3$) 0.69 (6 H, q, *J* 8.0, –SiCH_2CH$_3$), 1.00 (9 H, t, *J* 8.0, –SiCH$_2$CH_3), 2.04–2.11 (1 H, m, H4), 2.53 (1 H, ddd, *J* 2.4, 10.1 and 17.7, H3), 2.63 (1 H, ddd, *J* 9.6, 10.9 and 17.7, H3), 2.88–2.97 (1 H, m, H4), 4.35 (1 H, d, *J* 4.9, H10), 4.80 (1 H, t, *J* 5.2, H9), 6.13 (1 H, d, *J* 9.8, H7), 7.08 (1 H, dd, *J* 5.2 and 10.1, H8); δ_C (125 MHz, $CDCl_3$) 4.7 (–SiCH$_2$CH$_3$, × 3), 6.6 (–SiCH$_2$*C*H$_3$, × 3), 25.3 (C4), 27.1 (C3), 46.9 (C9), 68.6 (C10), 88.1 (C5), 127.0 (C7), 145.2 (C8), 175.5 (CO_2), 194.5 (CO); HRMS (EI) calcd for $C_{15}H_{23}{}^{79}BrO_4Si$ [M^+] 374.0549. Found 374.0537. *trans*-**15**: colourless oil; R_f (hexane–EtOAc 1 : 1) 0.65; δ_H (500 MHz, $CDCl_3$) 0.73 (6 H, q, *J* 7.9, –SiCH_2CH$_3$), 0.98 (9 H, t, *J* 7.9, –SiCH$_2$CH_3), 1.87 (1 H, ddd, *J* 3.4, 8.8 and 12.5, H4), 2.53–2.60 (2 H, m, H3), 2.70 (1 H, ddd, *J* 10.1, 10.4 and 12.5, H4), 4.49 (1 H, d, *J* 8.4, H10), 4.67 (1 H, dt, *J* 2.1 and 8.4, H9), 6.05 (1 H, dd, *J* 2.4 and 10.4, H7), 7.05 (1 H, dd, *J* 2.1 and 10.4, H8); δ_C (125 MHz, $CDCl_3$) 4.9 (–Si*C*H$_2$CH$_3$, × 3), 6.7 (–SiCH$_2$*C*H$_3$, × 3), 22.7 (C4), 26.8 (C3), 49.0 (C9), 76.7 (C10), 88.5 (C5), 126.0 (C7), 148.1 (C8), 174.9 (CO_2), 194.2 (CO); HRMS (EI) calcd for $C_{15}H_{23}{}^{79}BrO_4Si$ [M^+] 374.0549. Found 374.0564. **14′**: colourless oil; R_f (hexane–EtOAc 1 : 1) 0.7; δ_H (500 MHz, $CDCl_3$) 0.63 (6 H, q, *J* 7.9, –SiCH_2CH$_3$), 0.95 (9 H, t, *J* 7.9, –SiCH$_2$CH_3), 1.92–1.99 (1 H, m, H4), 2.49 (1 H, ddd, *J* 2.7, 9.4 and 19.2, H9), 2.54–2.70 (3 H, m, H3 × 2, H9), 2.76 (1 H, ddd, *J* 5.5, 6.7 and 18.9, H4), 4.37 (1 H, dd, *J* 5.5 and 9.1, H10), 7.33 (1 H, dd, *J* 2.7 and 6.4, H8); HRMS (EI) calcd for $C_{15}H_{23}{}^{79}BrO_4Si$ [M^+] 374.0549. Found 374.0535.

3-(1,2-Dihydroxy-6-triethylsilyloxy-3-cyclohexenyl)propanol (16)

To Et_2O (180 cm^3) at 0 °C was added $LiAlH_4$ (873.8 mg, 23.0 mmol). After 15 min, a solution of **13** (2.30 g, 7.67 mmol) in Et_2O (50 cm^3) was slowly added to the suspension and the resulting mixture was stirred at 0 °C for 30 min. After diluting with Et_2O and H_2O, the precipitate that formed was filtered. The filtrate was evaporated and the residue was purified by preparative TLC (silica gel, hexane–EtOAc 1 : 2) to give **16** (2.03 g, 87%) as a colourless oil: R_f (hexane–EtOAc 1 : 3) 0.3; ν(thin film)/cm^{-1} 3395, 2954, 2913, 2876; δ_H (500 MHz, $CDCl_3$) 0.62 (6 H, q, *J* 8.0, –SiCH_2CH$_3$), 0.97 (9 H, t, *J* 8.0, –SiCH$_2$CH_3), 1.52 (1 H, ddd, *J* 6.1, 7.9 and 14.0, H3), 1.65–1.74 (1 H, m, H2), 1.74–1.83 (1 H, m, H2), 1.87 (1 H, ddd, *J* 6.1, 8.2 and 14.0, H3), 2.06 (1 H, ddd, *J* 2.2, 8.0 and 16.8, H5′), 2.43 (1 H, dddd, *J* 0.9, 2.6, 5.4 and 16.8, H5′), 3.63–3.73 (2 H, m, CH_2OH), 4.09 (1 H, t, *J* 1.8, H2′), 4.11 (1 H, dd, *J* 5.4 amd 8.0, H6′), 5.73–5.75 (2 H, m, H3′, H4′), the hydroxy groups (3 H) were not observed due to broadening of the signals; δ_C (125 MHz, $CDCl_3$) 5.0 (–Si*C*H$_2$CH$_3$, × 3), 6.8 (–SiCH$_2$*C*H$_3$, × 3), 25.9 (C3), 28.5 (C2), 33.0 (C5′), 63.5 (C1), 69.5 (C6′), 70.2 (C2′), 74.0 (C1′), 127.3 (C3′), 128.0 (C4′); HRMS (FAB$^+$) calcd for $C_{15}H_{31}O_4Si$ [M + H] 303.1992. Found 303.1989.

3-(1,2-Dihydroxy-6-triethylsilyloxy-3-cyclohexenyl)propyl-2,2-dimethylpropanoate (17)

To a solution of **16** (1.09 g, 3.61 mmol) in pyridine (18 cm^3) was added PivCl (0.85 cm^3, 9.95 mmol) at 0 °C. The reaction mixture was stirred at 0 °C to rt for 4 h, quenched with sat. NH_4Cl, and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography (silica gel, hexane–EtOAc 6 : 1) to give **17** (1.24 g, 89%) as a colourless oil: R_f (hexane–EtOAc 2 : 1) 0.4; ν(thin film)/cm^{-1} 3458, 2958, 2911, 2876, 1729; δ_H (500 MHz, $CDCl_3$) 0.62 (6 H, q, *J* 7.9, –SiCH_2CH$_3$), 0.97 (9 H, t, *J* 7.9, –SiCH$_2$CH_3), 1.19 (9 H, s, C(CH$_3$)$_3$), 1.38 (1 H, ddd, *J* 4.4, 11.4 and 13.2, H3), 1.64–1.73 (1 H, m, H2), 1.75–1.92 (2 H, m, H2, H3), 2.04 (1 H, dddd, *J* 1.7, 2.6, 8.7 and 17.7, H5′), 2.42 (1 H, ddd, *J* 2.4, 5.6 and 17.7, H5′), 4.06 (2 H, t, *J* 6.6, CH_2OH), 4.09–4.10 (1 H, m, H2′), 4.12 (1 H, dd, *J* 5.6 and 8.7, H6′), 5.74–5.76 (2 H, m, H3′, H4′), the hydroxy groups (2 H) were not observed due to broadening of the signals; δ_C (125 MHz, $CDCl_3$) 5.0 (–Si*C*H$_2$CH$_3$, × 3), 6.7 (–SiCH$_2$*C*H$_3$, × 3), 22.4 (C3), 27.1 (C(*C*H$_3$)$_3$, × 3), 31.5 (*C*(CH$_3$)$_3$), 33.3 (C2), 38.6 (C5′), 64.8 (C1), 68.9 (C1′), 70.0 (C2′), 74.3 (C6′), 126.9 (C3′), 128.6 (C4′), 178.5 (CO_2); HRMS (EI) calcd for $C_{20}H_{38}O_5Si$ [M^+] 386.2489. Found 386.2476; anal. calcd for $C_{20}H_{38}O_5Si$: C, 62.14; H, 9.91%. Found: C, 62.22; H, 10.19%.

3-(1-Hydroxy-2-oxo-6-triethylsilyloxy-3-cyclohexenyl)propyl-2,2-dimethylpropanoate (18)

A solution of **17** (22.7 mg, 0.059 mmol) in DMSO (0.25 cm^3) was added to a solution of IBX (27.3 mg, 0.097 mmol) in DMSO (0.25 cm^3) at rt. The reaction mixture was stirred at rt for 1 h, quenched with H_2O and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by preparative TLC (silica gel, hexane–EtOAc 4 : 1) to give **18** (20.8 mg, 92%) as a colourless oil: R_f (hexane–AcOEt 4 : 1) 0.5; ν(thin film)/cm^{-1} 3492, 2957, 2911, 2875, 1728, 1684; δ_H (500 MHz, $CDCl_3$) 0.57–0.70 (6 H, m, –SiC$H_2$$CH_3$), 0.96 (9 H, t, *J* 7.8, –SiCH$_2$CH_3), 1.17 (9 H, s, *J* 7.8, C(CH_3)$_3$), 1.27–1.37 (1 H, m, H2), 1.52 (1 H, ddd, *J* 4.6, 11.6 and 14.0, H3), 1.72–1.81 (1 H, m, H2), 2.08 (1 H, ddd, *J* 4.6, 12.5 and 14.0, H3), 2.48 (1 H, ddt, *J* 2.5, 9.4 and 19.4, H5′), 2.63 (1 H, dt, *J* 5.8 and 19.5, H5′), 3.61 (1 H, s, OH), 4.00 (1 H, dd, *J* 5.9 and 9.5, H6′), 4.02 (2 H, t, *J* 6.5, H3), 6.07 (1 H, dd, *J* 2.5 and 10.1, H3′), 6.87 (1 H, ddd, *J* 2.5, 5.8 and 10.1, H4′); δ_C (125 MHz, $CDCl_3$) 4.9 (–SiCH$_2$CH$_3$, × 3), 6.8 (–SiCH$_2$$CH_3$, × 3), 22.1 (C3), 26.2 (C2), 27.1 (C(CH$_3$)$_3$, × 3), 35.2 (C5′), 38.7 (C(CH$_3$)$_3$), 64.3 (C1), 74.5 (C6′), 80.0 (C1′), 126.7 (C3′), 148.1 (C4′), 178.4 (CO_2), 202.2 (CO); HRMS (EI) calcd for $C_{20}H_{36}O_5Si$ [M^+] 384.2332. Found 384.2331; anal. calcd for $C_{20}H_{36}O_5Si$: C, 62.46; H, 9.44%. Found: C, 62.24; H, 9.42%.

3-(5-Bromo-1-hydroxy-2-oxo-6-triethylsilyloxy-3-cyclohexenyl)propyl-2,2-dimethylpropanoate (19)

To a solution of **18** (99.6 mg, 0.26 mmol) in CCl_4 (2.5 cm^3) was added recrystallized NBS (69.4 mg, 0.39 mmol) and AIBN (3.4 mg, 0.021 mmol). The reaction mixture was heated at 80 °C. After 1 h, the precipitate was filtered and the filtrate was evaporated. The residue was purified by preparative TLC (silica gel, hexane–CH_2Cl_2 1 : 2, × 4) to give **19** along with recovered **18** (**18**: 42.6 mg, 43%, **19**: 37.4 mg, 32%). **19**: Colourless oil: R_f (hexane–EtOAc 4 : 1) 0.6; ν(thin film)/cm^{-1} 3487, 2957, 2876, 1696, 1689, 1413, 1157, 738; δ_H (500 MHz, $CDCl_3$) 0.68–0.77 (6 H, m, –SiC$H_2$$CH_3$), 0.99 (9 H, t, *J* 7.9, –SiCH$_2$CH_3), 1.17 (9 H, s, C(CH_3)$_3$), 1.20–1.30 (1 H, m, H2), 1.42 (1 H, ddd, *J* 4.6, 11.6 and 13.8, H3), 1.68–1.75 (1 H, m, H2), 2.16 (1 H, ddd, *J* 4.6, 12.5 and 13.8, H3), 3.99 (2 H, t, *J* 6.4, H1), 4.11 (1 H, d, *J* 8.2, H6′), 4.72 (1 H, dt, *J* 2.4 and 8.2, H5′), 6.03 (1 H, dd, *J* 2.4 and 10.4, H3′), 6.97 (1 H, dd, *J* 2.4 and 10.4, H4′), the hydroxy group (1 H) was not observed due to broadening of the signal; δ_C (125 MHz, $CDCl_3$) 5.0 (–SiCH$_2$CH$_3$, × 3), 6.9 (–SiCH$_2$$CH_3$, × 3), 22.0 (C3), 27.2 (C(CH$_3$)$_3$, × 3), 27.4 (C2), 38.7 (C(CH$_3$)$_3$), 51.1 (C5′), 63.9 (C1), 81.1 (C1′), 82.2 (C6′), 125.3 (C3′), 148.1 (C4′), 178.4 (CO_2), 201.3 (CO); HRMS (FAB+) calcd for $C_{20}H_{36}{}^{79}BrO_5Si$ [M + H] 463.1515. Found 463.1509; anal. calcd for $C_{20}H_{35}BrO_5Si$: C, 51.83; H, 7.61%. Found: C, 51.76; H, 7.49%.

3-(5,6-Epoxy-1-hydroxy-2-oxo-3-cyclohexenyl)propyl-2,2-dimethylpropanoate (20)

TBAF (1.0 M in THF, 0.07 cm^3, 0.07 mmol) was added to a solution of **19** (30.7 mg, 0.066 mmol) in THF (0.7 cm^3) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. After diluting with sat. NH_4Cl, the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by preparative TLC (silica gel, hexane–EtOAc 3 : 2) to give **20** (14.5 mg, 82%) as a colourless oil: R_f (hexane–EtOAc 1 : 1) 0.3; ν(thin layer)/cm^{-1} 3444, 2973, 1723, 1685, 1287; δ_H (500 MHz, $CDCl_3$) 1.20 (9 H, s, C(CH_3)$_3$), 1.75 (1 H, td, *J* 2.3 and 10.7, H3), 1.79–1.89 (1 H, m, H3), 1.89–1.99 (2 H, m, H2), 2.74 (1 H, s, OH), 3.49 (1 H, td, *J* 0.9 and 3.7, H5′), 3.66 (1 H, dd, *J* 0.9 and 3.7, H6′), 4.07–4.15 (2 H, m, H1), 6.13 (1 H, dd, *J* 1.2 and 10.4, H3′), 7.12 (1 H, ddd, *J* 0.9, 3.7 and 10.4, H4′); δ_C (125 MHz, $CDCl_3$) 22.3 (C2), 27.2 (C(CH$_3$)$_3$, × 3), 33.1 (C3), 38.8 (C(CH$_3$)$_3$), 46.5 (C5′), 59.4 (C6′), 64.2 (C1), 73.7 (C1′), 130.5 (C3′), 144.0 (C4′), 178.6 (CO_2), 198.5 (CO); HRMS (FAB$^+$) calcd for $C_{14}H_{21}O_5$ [M + H] 269.1389. Found 269.1374; anal. calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51%. Found: C, 62.55; H, 7.71%.

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9 (*a*) Details on the Diels–Alder reaction of **2** with cyclopentadiene will be reported in due course. The relative stereochemistry of **3a** and **3b** was determined by ^{1}H NMR NOE experiments. A tentative explanation for the reversal in the facial selectivity of the epoxidation of the Diels–Alder adducts is that while the methylene group of the spiro–lactone ring placed at a pseudo-axial position of the enone ring in the transition state for **3a**, it is placed at a pseudo-equatrial position in the case of **3b** to avoid repulsion between the CbzNH group and

the reagent; (*b*) spectral data of **3a**: δ_H (500 MHz, $CDCl_3$) 1.25 (1 H, dd, *J* 2.3 and 7.7), 1.47 (1 H, d, *J* 7.7), 2.59 (1 H, t, *J* 12.9), 2.83 (1 H, d, *J* 13.1), 3.05 (1 H, dd, *J* 9.4 and 12.9), 3.11 (1 H, s), 3.13 (1 H, d, *J* 13.1), 3.14 (1 H, s), 3.35 (1 H, d, *J* 3.4), 3.37 (1 H, d, *J* 3.9), 4.48 (1 H, ddd, *J* 6.4, 9.4 and 12.9), 5.15 (2 H, bs), 5.55 (1 H, d, *J* 6.4), 6.05 (1 H, bs), 6.13 (1 H, bs), 7.31–7.42 (5 H, m); δ_C (125 MHz, $CDCl_3$) 38.3, 42.9, 43.9, 48.5, 48.6, 50.0 (× 2), 55.3, 58.9, 67.5, 81.8, 128.3(× 2), 128.5, 128.7 (× 2), 133.7, 135.7, 136.0, 155.9, 172.4, 205.0; HRMS (EI) calcd for $C_{22}H_{21}NO_6$ [M^+] 395.1369; found 395.1360; anal.calcd for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35; N, 3.54%. Found: C, 66.71; H, 5.55; N, 3.48%; (*c*) spectral data of **3b**: δ_H (500 MHz, $CDCl_3$) 1.30 (1 H, d, *J* 8.2), 1.50 (1 H, d, *J* 8.2), 2.72 (1 H, t, *J* 12.9), 2.86–3.04 (3 H, m), 3.09–3.23 (2 H, m), 3.36 (1 H, bs), 3.56 (1 H, bs), 4.52 (1 H, dd, *J* 10.1 and 15.5), 5.13 (2 H, s), 5.49 (1 H, bs), 5.85 (1 H, dd, *J* 3.2 and 5.5), 6.17 (1 H, dd, *J* 2.4 and 5.5), 7.30–7.43 (5 H, m); δ_C (125 MHz, $CDCl_3$) 41.1, 42.4, 44.4, 49.3 (× 2), 49.8, 51.1, 55.0, 61.7, 67.7, 82.5, 128.3 (× 2), 128.5, 128.7 (× 2), 134.3, 135.2, 135.7, 155.8, 172.8, 204.9; HRMS (EI) calcd for $C_{22}H_{21}NO_6$ [M^+] 395.1369; found 395.1385; anal. calcd for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35; N, 3.54%. Found: C, 66.87; H, 5.34; N, 3.54%.

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17 Bromination at the C4 position *via* enolization of **18** with LDA also failed.

18 The calculations were performed with PC Spartan Pro, Wavefunction, Inc., Irvine, CA 92715.