The First Synthesis of (−)-Asperpentyn and Efficient Syntheses of (+)-Harveynone, (+)-Epiepoformin and (−)-Theobroxide

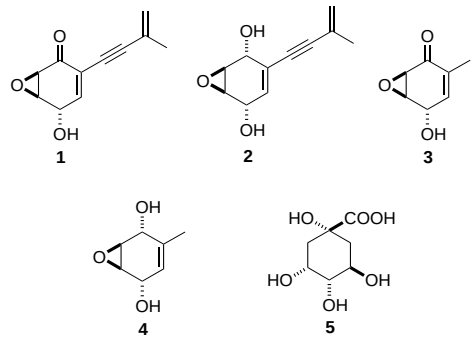
M. Teresa Barros,[a] Christopher D. Maycock,*[b] and M. Rita Ventura[b]

Abstract: A generally applicable strategy for the synthesis of a range of polyoxygenated cyclohexane natural products has been developed. The enantioselective syntheses of (−)-theobroxide, a polyoxygenated cyclohexane natural compound with potent growth inducing properties in potato microtubers has been achieved via a 1,2 *O*-silyl migration between *trans*-hydroxyl groups and a remote hydroxyl directed epoxidation of an enone derived from quinic acid. A thus derived α-iodoenone was subjected to Stille coupling with tetramethylstannane to afford the first title compound. A similar strategy enabled a route to the complete asymmetric synthesis of the acetylenic phytotoxin (+)-harveynone. By selective reduction of (−)-theobroxide, (+)-epiepoformin was also prepared in enantiopure form and similarly, stereoselective reduction of (+)-harveynone completed the first enantioselective synthesis of (−)-asperpentyn, another natural compound with antimicrobial activity.

Keywords: asymmetric synthesis · C–C coupling · natural products · palladium

Introduction

(+)-Harveynone (**1**), (−)-asperpentyn (**2**), (+)-epiepoformin (**3**) and (−)-theobroxide (**4**) belong to a family of highly oxygenated cyclohexane-based metabolites, mainly epoxides,



that have been isolated from bacteria, fungi, higher plants and molluscs. These compounds have stimulated several synthetic efforts[2, 5, 7–10] due to their biological activities, which range from antifungal to antibacterial, antitumor, phytotoxic and enzyme inhibition.[1–10]

(+)-Harveynone (**1**) has been isolated from the tea gray blight fungus *Pestalotiopsis theae* and shown to be a phytotoxin.[1] Related compound (−)-asperpentyn (**2**) has been isolated from the antimicrobial extracts of *Aspergillus duricaulis*.[3] These natural compounds both contain an acetylenic side chain, which is a characteristic feature of many members of the polyoxygenated cyclohexane family. (+)-Epiepoformin (**3**) has been isolated from the culture filtrate of an unidentified fungus of the deceased leaf of crape myrtle *Lagerstroemia indica*,[6] and (−)-theobroxide (**4**) has been isolated from *Lasiodiplodia theobromae* and shows exceptional activity as a potato microtuber inducing substance.[4] The rarity and diverse biological activities of these compounds has prompted us to devise a strategy which should be generally applicable to their synthesis, and the synthesis of derivatives, in an enantiopure form and eventually their preparation in useful quantities for biological testing.

(+)-Harveynone has been asymmetrically synthesised by Johnson and co-workers[2a] and, in a racemic form, by Taylor and co-workers.[2b] There is also only one synthesis of theobroxide described in the literature so far,[5] and two syntheses[5, 7] of epiepoformin, one of them racemic,[7] the other relied upon a retro-Diels-Alder reaction for the liberation of the unsaturated product.[5] To our knowledge, (−)-asperpentyn has not been previously synthesised and our synthesis confirms the structure proposed after its isolation.[3]

(−)-Quinic acid (**5**), an abundant natural substance has, besides a cyclohexane skeleton, a masked 1,4-oxygen functionality suitable for synthesis of the necessary hydroxyl and

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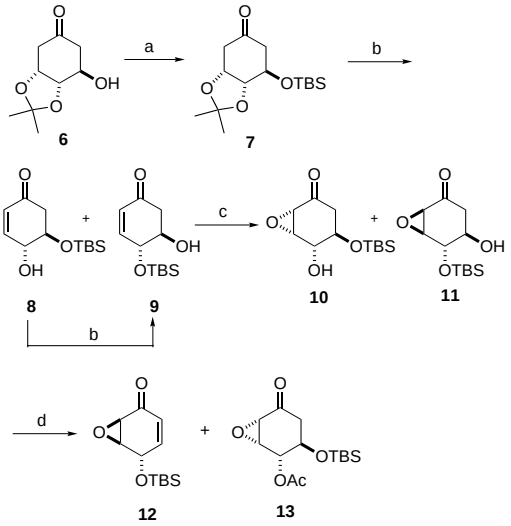
carbonyl groups in these positions of the target compounds. This characteristic 1,4-substitution is present in all compounds, for which the synthesis is described herein, and in many other members of the polyoxygenated cyclohexane metabolite family. (−)-Quinic acid also contains hydroxyl functions which are ideally situated for the sequential generation of the necessary enones. Its structure can be transformed selectively in diverse ways and has permitted its use in many other syntheses.[8, 9, 11–19] Other advantages are the accessibility and relatively low cost of (−)-quinic acid.

Results and Discussion

Our strategy was based on two sequential β-eliminations which allowed the formation of two enone systems, one necessary for the introduction of the epoxide group and the other to remain in the final structure of our target compounds. In Scheme 1 the initial common steps for these syntheses are depicted.

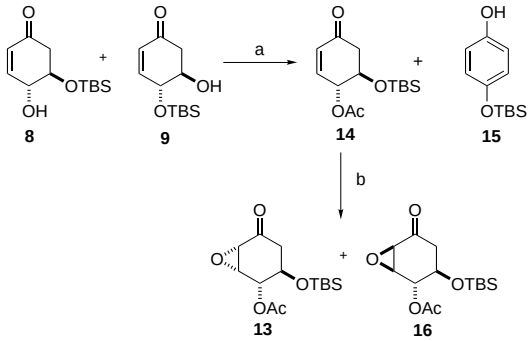


Scheme 1. a) TBSCl, imidazole, DMF, 35 °C, 98%. b) 0.5 N NaOH, THF, 0 °C, 82% (1:1 **8**:**9**). c) 30% H_2O_2, Triton B, THF, 0 °C, 89%. d) Ac_2O, $(iPr)_2NEt$, DMAP, CH_2Cl_2, 0 °C, 44% of **12** and 42% of **13**.

Abstract in Portuguese: *Uma estratégia geral para a síntese de produtos naturais com estrutura de ciclohexano polioxigenado foi desenvolvida. A síntese do (−)-teobróxido, um composto natural com potentes propriedades na indução do crescimento dos microtubérculos de batatas, foi efectuada via uma migração 1,2 O-sililo entre grupos hidroxilos trans e uma epoxidação, orientada remotamente por um hidroxilo, de uma enona derivada do ácido quínico. A α-iodoenona obtida foi submetida a um acoplamento de Stille com tetrametilestanano, para originar o produto referido. Uma estratégia similar permitiu a síntese assimétrica completa da fitotoxina acetilénica (+)-harveinona. Através da redução selectiva do (−)-teobróxido, a (+)-epiepoformina foi igualmente preparada na forma enantiopura e, da mesma maneira, a redução estereosselectiva da (+)-harveynona completou a primeira síntese enantiosselectiva da (−)-asperpentina, outro composto natural com actividade antimicrobiana.*

β-Hydroxyketone **6** was obtained in three steps from (−)-quinic acid (**5**) in excellent yields, as previously described in the literature.[8] Silylation of **6** afforded the protected compound **7** in 98% yield, which upon treatment with 0.5 N NaOH[8, 17] furnished a mixture of two compounds later identified as the anticipated product enone **8** and the isomeric enone **9**, in approximately 1:1 ratio. The NMR spectra of **8** and **9** were very similar as would be expected. They were identified by treating each separately with acetic anhydride whereupon the less polar isomer becomes aromatic to form compound **15**; this indicates that indeed β-hydroxyketone **9** was formed. The acetate **13** was obtained from the other isomer **8** after epoxidation and elimination. The enone **9** clearly resulted from an unusual silyl migration between the *trans* diequatorial hydroxyl groups which was promoted by the alkoxide formed during elimination. Attempts to transform all of compound **8** into **9** in one reaction with a base failed,[20] which indicated that an equilibrium was established between the two products. The separation of these isomers permitted a recycling of isomer **8** with a base, and an increase in the overall yield. Thus, treatment of isomer **8** with a catalytic quantity of hydroxide in THF afforded again a 1:1 mixture of these isomers in quantitative yield. After one recycle about 75% of the required **9** could be obtained. The formation of enone **9** in this way was not predictable but nevertheless turned out to be a key compound.

Epoxidation of the mixture of enones **8** and **9** with 30% hydrogen peroxide in the presence of Triton B afforded an inseparable mixture of only the two epoxides **10** and **11** (Scheme 1). In accordance with our previous observations[9] the attack of the epoxidising agent upon the double bond was directed by the free hydroxyl group in the molecule. Thus, the hydroxyl group of enone **8**, being below the plane of the molecule, as drawn in Scheme 1, directed the peroxide to the lower face of the enone system with subsequent formation of the epoxide **10**. A similar directing effect was observed for the epoxidation of **9** which gave the epoxide **11**, where both the hydroxyl and the epoxide groups were *cis* and above the plane of the molecule as drawn. The importance of the free hydroxyl group in these oxidations was demonstrated by the epoxidation of the acetate **14**, obtained by treatment of **8** with acetic anhydride and DMAP in pyridine at 0 °C. This epoxidation, employing the bulky *t*BuOOH, afforded a 1:1 mixture of the two diastereoisomers **13** and **16** (Scheme 2). Thus the absence of the free hydroxyl group drastically reduced the selectivity of the epoxidation reaction.



Scheme 2. a) Ac_2O, py, DMAP, 0 °C. b) *t*BuOOH, Triton B, THF, 0 °C.

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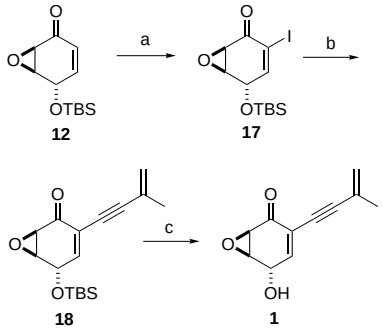
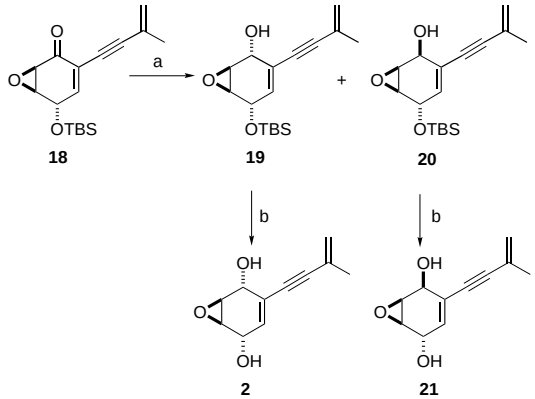
Elimination of water in compound **11** was carried out by acetylation of a 1:1 mixture of **10** and **11** which led to enone **12** and the acetylated product **13** (Scheme 1). These two products were easily separable by simple chromatography which afforded **12** (44%) $[\alpha]_D^{28} = +331.5$ ($c = 1.22$, anhydrous $CHCl_3$);[10b] *ent*-**12**: $[\alpha]_D^{28} = -333.3$ ($c = 1.32$, $CHCl_3$), and **13** (42%).

α-Iodination of enone **12** afforded iodoenone **17** (Scheme 3) in excellent yields (93%), $[\alpha]_D^{28} = +108.6$ ($c = 1.19$, anhydrous $CHCl_3$);[10b] *ent*-**17**: $[\alpha]_D^{29} = -109.7$ ($c = 1.29$, $CHCl_3$). With the Stille cross-coupling reaction the acetylenic side chain could be introduced in 98% yield. Johnson[2a] used a Sonogashira coupling reaction instead of the Stille methodology to perform the same reaction but only in 52% yield. Desilylation of the coupled product **18** with 40% wt HF in H_2O afforded (+)-harveynone (**1**) in 92% yield (42% overall from **6**),[21] ($[\alpha]_D^{20} = +206.6$ ($c = 0.38$, anhydrous MeOH);[2a] *ent*-**1**: $[\alpha]_D = -208$ ($c = 0.45$, MeOH)). The spectroscopic data for our synthetic product is in accordance with those reported in the literature.[2b]



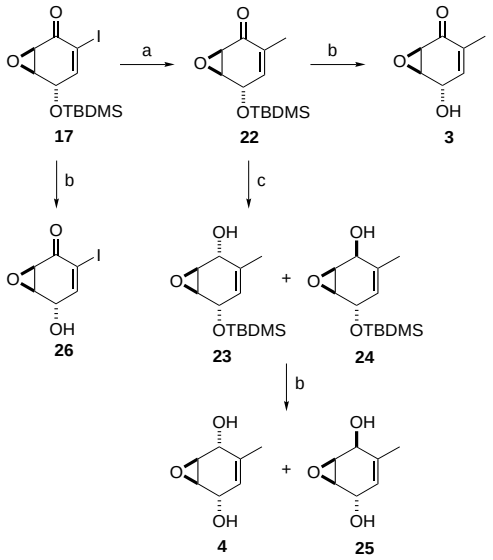
Scheme 3. a) I_2, DMAP, CCl_4/py 1:1, 0°C/RT, 93%. b) $Bu_3SnC{\equiv}C\text{-}C(CH_2)CH_3$, CuI, $AsPh_3$, $Pd(PPh_3)_2Cl_2$, THF, RT, 98%. c) HF (40% in H_2O), CH_3CN, RT, 92%.

In order to synthesise (−)-asperpentyn (**2**) we required a selective method for the reduction of the carbonyl group of enone **18** (Scheme 4). DIBAL-H in THF at −78°C afforded both possible diastereoisomers with an unsatisfying *dr* of only 1:1. By performing the same reaction with sodium borohydride and cerium(III) chloride we were able to increase the diastereoselectivity to 2.7:1 **19**:**20**. Deprotection of both alcohols afforded (−)-asperpentyn (**2**) ($[\alpha]_D^{20} = -17.1$ ($c = 0.28$, acetone),[3] $[\alpha]_D^{20} = -20$ ($c = 0.1$, acetone)) (33% overall from **6**) and its epimer **21**. The NMR data were in accord with the literature[3] although both diastereoisomers had very similar spectra.



Scheme 4. a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78°C, 99% yield, *dr* 2.7:1 **19**:**20**. b) HF (40% in H_2O), CH_3CN, RT, quantitative.

The two other target molecules were (+)-epiepoformin and (−)-theobroxide. We have already synthesised (+)-epoformin[9] from (−)-quinic acid by a less direct route. A Stille cross-coupling reaction was used to introduce the methyl group into α-iodoenone **17** (Scheme 5).



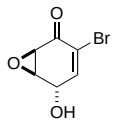
Scheme 5. a) Me_4Sn, $AsPh_3$, $Pd_2(dba)_3 \cdot CHCl_3$, CuI, THF, 80°C, 91%. b) HF (40% in H_2O), CH_3CN, RT, 99%. c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78°C, 92%.

There are very few examples for the introduction of alkyl groups employing Stille cross-coupling reactions described in the literature;[22] especially for α-iodocyclohexenones the reported yields are rather low. Usually these reactions are carried out in relatively non-volatile dipolar solvents such as DMF or NMP. In our case (Scheme 5), we employed THF as the solvent. Iodoenone **17** was treated with $Pd_2(dba)_3 \cdot CHCl_3$, $AsPh_3$, CuI and Me_4Sn in a sealed tube and we were able to obtain the α-methylated enone **22** in 91% yield, $[\alpha]_D^{28} = +251.3$ ($c = 1.40$, anhydrous $CHCl_3$),[5] $[\alpha]_D^{28} = +250.72$ ($c = 1.17$, $CHCl_3$). Work-up was, however, complicated by the appearance of what we believe to be colloidal palladium which contaminated the product even after chromatography. This problem was resolved by using Et_2NH, while at the same time eliminating the use of cuprous iodide. The reaction was accelerated by the addition of 3 equivalents of diethylamine. Desilylation of **22** with 40% HF in H_2O, furnished in acetonitrile (+)-epiepoformin (**3**), $[\alpha]_D^{28} = +314.5$ ($c = 0.49$, EtOH),[5] $[\alpha]_D^{28} = +316.4$ ($c = 0.37$, EtOH), in 99% yield (42% overall from **6**) (Scheme 5). The ^1H NMR spectrum was identical to that reported in the literature.[5] Reduction of the α,β-unsaturated ketone **22** with sodium borohydride in the presence of cerium(III) chloride afforded the two diastereoisomers **23** and **24** (Scheme 5),[5] which were unseparable by standard chromatographic techniques. However, after deprotection with 40% HF, (−)-theobroxide (**4**), $[\alpha]_D^{28} = -6.18$ ($c = 0.35$, EtOH),[5] $[\alpha]_D^{28} = -6.25$ ($c = 0.40$, EtOH), and its epimer **25**, $[\alpha]_D^{28} = +48.57$ ($c = 0.35$, EtOH),[3] $[\alpha]_D^{28} = +47.52$ ($c = 0.59$, EtOH), were obtained in 84% (40% overall from **6**)

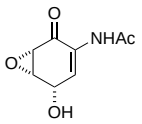
and 15% yields, respectively. (+)-Iodoxone (**26**), $[\alpha]_D^{20} = +94.8$ ($c = 0.61$, anhydrous acetone),[2a] $[\alpha]_D = +96.1$ ($c = 0.95$, acetone), an analogue of the natural compound (+)-bromoxone[10b] was also obtained after cleavage of the silyl ether of α-iodoenone **17** (47% overall yield from **6**) (Scheme 5).

Conclusion

In summary, an efficient methodology was developed to synthesise four related natural compounds with high enantiopurity. The use of common intermediates readily derived from quinic acid combined with a Stille coupling reaction should permit the synthesis of a wide range of cyclohexane based natural products. This methodology should also be applicable to the synthesis of more complex members of the polyoxygenated cyclohexane family. From compound **13**, the antibiotic LL-C10037α and several members of the manumycin family of antibiotics[10e] may also be accessible using a little used aza Stille cross-coupling reaction to introduce the amide side chain. Our studies in this promising area are currently under way.



(+)-Bromoxone



LL-C10037α

Experimental Section

General methods: Melting points were determined with a capillary apparatus and are uncorrected. ^{1}H NMR spectra were obtained at 300 MHz in $CDCl_3$ with chemical shift values (δ) in ppm downfield from tetramethylsilane, and ^{13}C NMR spectra were obtained at 100.61 MHz in $CDCl_3$. DEPT was used to aid the structure elucidation and carbon assignments but the data are not reported here. Microanalyses were performed by the IST analytical services using a combustion apparatus. IR ($\tilde{\nu}$, cm^{-1}) measured on a FTIR spectrophotometer. Medium pressure preparative column chromatography: silica gel Merck 60H. Preparative TLC: silica gel Merck 60 GF_{254}. Analytical TLC: Aluminum-backed silica gel Merck 60 F_{254}. Specific rotations ($[\alpha]$) were measured on an automatic polarimeter. Reagents and solvents were purified and dried according to ref. [23]. All the reactions were carried out in an inert atmosphere (argon), unless otherwise indicated.

(3*R*,4*R*,5*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-3,4-(isopropylidenedioxy)-1-cyclohexanone (7): Imidazole (0.92 g, 0.014 mol) and TBSCl (1 g, 6.4 mmol) were added to a solution of **6** (1 g, 5.37 mmol) in DMF (3 mL). The reaction mixture was stirred for 24 h at 35 °C and, after cooling, water was added (4 mL) and the pH adjusted to 8 if necessary. The mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phases were dried ($MgSO_4$) and concentrated. The viscous residue was purified by column chromatography (CH_2Cl_2) to afford ketone **7** (1.61 g, 98%) as a colourless oil that crystallised at low temperatures. $[\alpha]_D^{20} = +93.1$ ($c = 2.60$, CH_2Cl_2); m.p. 37–38 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 300 K, TMS): $\delta =$ 4.70 (dt, ^3J(H,H) = 6.6 Hz, ^3J(H,H) = 3.0 Hz, 1H, H-3), 4.21 (dt, ^3J(H,H) = 6.9 Hz, ^3J(H,H) = 2.1 Hz, 1H, H-4), 4.16 (d, ^3J(H,H) = 3.0 Hz, 1H, H-5), 2.76 (dd, ^2J(H,H) = 17.7 Hz, ^3J(H,H) = 3.6 Hz, 1H, H-2), 2.64 (dd, ^2J(H,H) = 19.5 Hz, ^3J(H,H) = 2.1 Hz, 2H, H-2/H-6), 2.37 (dd, ^2J(H,H) = 17.4 Hz, ^3J(H,H) = 3.3 Hz, 1H, H-6), 1.44 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 0.85 (s, 9H, SiC(CH_3)$_3$), 0.09, 0.06 (2s, 2 × 3H, 2 × SiCH_3); ^{13}C NMR (100.61 MHz, $CDCl_3$, 300 K, TMS): $\delta = 207.8$ (C-1), 108.7 ($C(CH_3)_2$), 75.1, 72.3, 68.7 (C-3, C-4, C-5), 41.7, 40.0 (C-2, C-6), 26.1 (CH_3), 25.4 (SiC(CH_3)$_3$), 23.7 (CH_3), 17.6 (SiC(CH_3)$_3$), −5.3 (2 × SiCH_3); FT-IR (KBr): $\tilde{\nu} = 1722$ (C=O, sat. ketone); elemental analysis calcd (%) for $C_{15}H_{28}O_4Si$ (300.47351): C 59.96, H 9.39; found: C 59.83, H 8.09.

(4*R*,5*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-4-hydroxy-2-cyclo-hexen-1-one (8) and (4*R*,5*R*)-4-[(*tert*-butyldimethylsilyl)oxy]-5-hydroxy-2-cyclohexen-1-one (9): A catalytic amount of aqueous NaOH (0.5 N) was added at 0 °C to a solution of **7** (1.193 g, 3.97 mmol) in THF (10 mL). The mixture was stirred at 0 °C until all starting material was consumed (if the reaction slowed down, five more drops of aqueous 0.5 N NaOH were added). Saturated aqueous NH_4Cl was added (6 mL), and the mixture was extracted with diethyl ether (3 × 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated. The residue obtained was purified by column chromatography (AcOEt/hexane 1:9) **8** (0.394 g, 41%) and **9** (0.396 g, 41%), compound **8** slowly crystallised, so that compound **7** could be recovered to some extent (0.167 g). Compound **8**: $[\alpha]_D^{20} = -145.8$ ($c = 0.26$, CH_2Cl_2); m.p. 64–66 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 300 K, TMS): $\delta =$ 6.89 (dd, ^3J(H,H) = 10.2 Hz, ^3J(H,H) = 1.8 Hz, 1H, H-3), 6.00 (d, ^3J(H,H) = 10.2 Hz, 1H, H-2), 4.36 (m, 1H, H-4), 3.98–3.90 (m, 1H, H-5), 2.74 (dd, ^2J(H,H) = 16.5 Hz, ^3J(H,H) = 4.8 Hz, 1H, H-6), 2.48–2.41 (m, 2H, H-6, O*H*), 0.91 (s, 9H, SiC(CH_3)$_3$), 0.13, 0.12 (2s, 2 × 3H, 2 × SiCH_3); ^{13}C NMR (100.61 MHz, $CDCl_3$, 300 K, TMS): $\delta = 197.5$ (C-1), 149.9, 129.6 (C-2, C-3), 73.9, 73.2 (C-4, C-5), 45.7 (C-6), 25.7 (SiC(CH_3)$_3$), 17.8 (SiC(CH_3)$_3$), −4.4, −4.7 (2 × SiCH_3); FT-IR (film): $\tilde{\nu} = 3400$ (O–H), 1675 (C=O, α,β-unsat. ketone); compound **9**: $[\alpha]_D^{20} = -128.1$ ($c = 0.27$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 300 K, TMS): $\delta = 6.73$ (dd, ^3J(H,H) = 10.2 Hz, ^3J(H,H) = 1.8 Hz, 1H, H-3), 5.97 (dt, ^3J(H,H) = 10.2 Hz, ^4J(H,H) = 2.1 Hz, ^4J(H,H) = 1.2 Hz, 1H, H-2), 4.33 (dt, ^3J(H,H) = 7.8 Hz, ^3J(H,H) = 2.1 Hz, 1H, H-4),; 4.00–3.91 (m, 1H, H-5), 2.84 (ddd, ^2J(H,H) = 16.5 Hz, ^3J(H,H) = 4.8 Hz, ^4J(H,H) = 1.2 Hz, 1H, H-6), 2.42 (dd, ^2J(H,H) = 16.5 Hz, ^3J(H,H) = 12.3 Hz, 1H, H-6), 2.35 (s, 1H, O*H*), 0.95 (s, 9H, SiC(CH_3)$_3$), 0.18 (s, 6H, 2 × SiCH_3); ^{13}C NMR (100.61 MHz, $CDCl_3$, 300 K, TMS): $\delta = 197.2$ (C-1), 151.1, 129.4 (C-2, C-3), 73.9, 72.7 (C-4, C-5), 43.7 (C-6), 25.7 (SiC(CH_3)$_3$), 18.0 (SiC(CH_3)$_3$), −4.5, −4.6 (2 × SiCH_3); FT-IR (film): $\tilde{\nu} = 3417$ (O–H), 1677 (C=O, α,β-unsat. ketone); HR-MS (EI$^+$): calcd for $C_{12}H_{22}O_3Si$ $[M]^+$: 242.133823; found: 242.133134.

A catalytic amount of aqueous NaOH (0.5 N) was added at 0 °C to a solution of **8** (0.039 g, 0.16 mmol) in THF (1 mL). The mixture was stirred at 0 °C for 1 h. Saturated aqueous NH_4Cl was added (3 mL), and the mixture was extracted with diethyl ether (3 × 4 mL). The organic extracts were dried ($MgSO_4$) and concentrated. The residue obtained was purified by preparative TLC (AcOEt/hexane 4:6) to yield **8** (0.019 g, 49%) and **9** (0.020 g, 51%), both as colourless oils; compound **8** did crystallise after some time.

(2*S*,3*R*,4*R*,5*R*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-4-hydroxy-1-cyclohexanone (10) and (2*R*,3*S*,4*S*,5*R*)-4-[(*tert*-butyldimethylsilyl)oxy]-2,3-epoxy-5-hydroxy-1-cyclohexanone (11): 30% H_2O_2 (3.67 mL, 0.032 mol) and Triton B (*N*-benzyltrimethylammonium hydroxide, 40 wt% solution in methanol, 0.104 mL, 0.25 mmol) was added at 0 °C to a solution of the mixture of enones **8** and **9** (1.039 g, 4.29 mmol) in THF (5 mL). After all starting material had been consumed, saturated aqueous NH_4Cl solution (5 mL) was added, and the mixture was extracted with diethyl ether (3 × 10 mL), the combined organic extracts were dried ($MgSO_4$), and evaporated to give a liquid residue, which was purified by column chromatography. Elution with AcOEt/hexane 2:8 afforded the epoxides **10** and **11** (1.244 g, 89%) as a colourless oil. Compounds **10** and **11**: ^{1}H NMR (300 MHz, $CDCl_3$, 300 K, TMS): $\delta = 4.27$ (dd, ^3J(H,H) = 4.8 Hz, ^3J(H,H) = 2.1 Hz, 1H, H-4), 4.11–4.05 (m, 1H, H-5), 3.96 (dd, ^3J(H,H) = 6.0 Hz, ^3J(H,H) = 2.4 Hz, 1H, H-4), 3.86–3.80 (m, 1H, H-5), 3.74–3.72 (m, 1H, H-2 or H-3), 3.57–3.55 (m, 1H, H-2 or H-3), 3.41–3.37 (m, 2H, H-2, H-3), 2.81 (dd, 1H, ^2J(H,H) = 16.8 Hz, ^3J(H,H) = 4.5 Hz, H-6), 2.65 (dd, ^2J(H,H) = 16.4 Hz, ^3J(H,H) = 3.9 Hz, 1H, H-6), 2.26–2.16 (m, 2H, 2 × H-6), 1.93 (br s, 1H, O*H*), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.87 (s, 9H, SiC(CH_3)$_3$), 0.17, 0.15, 0.10, 0.08 (4s, 4 × 3H, 4 × SiCH_3). FT-IR (film): $\tilde{\nu} = 3424$ (O–H), 1722 (C=O, sat. ketone); HR-MS (EI+): calcd for $C_{12}H_{22}O_4Si$ $[M]^+$: 258.128738; found: 258.128342.

(2*R*,3*S*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-5-cyclohexen-1-one (12) and (2*S*,3*R*,4*R*,5*R*)-4-acetyloxy-5-[(*tert*-butyldimethylsilyl)oxy]-2,3-epoxy-1-cyclohexanone (13): A catalytic amount of 4-(dimethylamino)pyridine (DMAP), diisopropylethylamine (1.53 mL, 9.16 mmol) and acetic anhydride (0.522 mL, 5.50 mmol) were added to a solution of **10** and **11** (1.184 g, 4.58 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After 90 min stirring at 0 °C, all starting material had been consumed. Saturated aqueous $NaHCO_3$

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(5 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 7 mL). After drying and concentrating the organic extracts, the residue was purified by column chromatography (AcOEt/hexane 0.5:9.5) to afford enone **12** (0.485 g, 44%) and protected compound **13** (0.578 g, 42%), both as colourless oils. Compound **12**: $[\alpha]_D^{28} = +331.5$ ($c = 1.22$, anhydrous $CHCl_3$),[10b] *ent*-**12**: $[\alpha]_D^{28} = -333.3$ ($c = 1.32$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 300 K, TMS): $\delta = 6.53$ (ddd, $^3J(H,H) = 10.5$ Hz, $^4J(H,H) = 4.2$ Hz, $^4J(H,H) = 2.4$ Hz, 1H, H-5), 5.96 (dt, $^3J(H,H) = 10.5$ Hz, $^3J(H,H) = 1.2$ Hz, 1H, H-6), 4.66 (dt, $^3J(H,H) = 4.5$ Hz, $^3J(H,H) = 1.2$ Hz, 1H, H-4), 3.66–3.64 (m, 1H, H-2 or H-3), 3.47–3.45 (m, 1H, H-2 or H-3), 0.93 (s, 9H, $SiC(CH_3)_3$), 0.19, 0.16 (2s, 2 × 3H, 2 × $SiCH_3$); ^{13}C NMR (100.61 MHz, $CDCl_3$, 300 K, TMS): $\delta = 193.1$ (C-1), 144.2, 126.2 (C-5, C-6), 63.6 (C-4), 58.3, 53.2 (C-2, C-3), 25.6 ($SiC(CH_3)_3$), 18.0 ($SiC(CH_3)_3$), −4.6, −4.7 (2 × $SiCH_3$); FT-IR (film): $\tilde{\nu} = 1692$ (C=O, α,β-unsat. ketone); HR-MS (EI+): calcd for $C_{12}H_{20}O_2Si$ $[M-O]^+$: 224.123258; found: 224.123822; compound **13**: $[\alpha]_D^{20} = -106.0$ ($c = 0.52$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 300 K, TMS): $\delta = 5.05$ (dd, $^3J(H,H) = 6.3$ Hz, $^3J(H,H) = 1.8$ Hz, 1H, H-4), 4.20 (m, 1H, H-5), 3.72–3.70 (m, 1H, H-3), 3.37 (d, $^3J(H,H) = 3.9$ Hz, 1H, H-2), 2.86 (dd, $^2J(H,H) = 17.1$ Hz, $^3J(H,H) = 4.8$ Hz, 1H, H-6), 2.27 (dd, $^2J(H,H) = 16.8$ Hz, $^3J(H,H) = 7.8$ Hz, 1H, H-6), 2.18 (s, 3H, $COCH_3$), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.08, 0.06 (2s, 2 × 3H, 2 × $SiCH_3$); FT-IR (film): $\tilde{\nu} =$ 1747 (C=O), 1727 (C=O); HR-MS (EI+) calcd for $C_{13}H_{24}O_5Si$ $[M-CH_3]^+$: 285.115827; found: 285.115791.

(2*R*,3*S*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-6-iodo-5-cyclohexen-1-one (17): I_2 (0.390 g, 1.56 mmol) in pyridine/CCl_4 (1 mL:1 mL) and a catalytic amount of DMAP were added at 0 °C to a solution of enone **12** (0.150 g, 0.62 mmol) in pyridine/CCl_4 (1 mL:1 mL). The reaction mixture was stirred at RT for 1 h, and then 20% aqueous $Na_2S_2O_3$ solution (4 mL) was added. The mixture was extracted with diethyl ether (3 × 10 mL), the combined organic extracts were washed with aqueous 5% $CuSO_4$, dried ($MgSO_4$) and concentrated to afford a liquid residue which was purified by preparative TLC. Elution with AcOEt/hexane 1:9 furnished **17** (0.213 g, 93%) as a colourless liquid. $[\alpha]_D^{28} = +108.6$ ($c = 1.19$, anhydrous $CHCl_3$);[10h] *ent*-**17**: $[\alpha]_D^{29} = -109.7$ ($c = 1.29$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 300 K, TMS): $\delta = 7.29$ (dd, $^3J(H,H) = 5.1$ Hz, $^4J(H,H) = 2.4$ Hz, 1H, H-5), 4.60 (ddd, $^3J(H,H) = 4.8$ Hz, $^3J(H,H) = 1.2$ Hz, $^4J(H,H) = 1.2$ Hz, 1H, H-4), 3.70–3.68 (m, 1H, H-2 or H-3), 3.64–3.62 (m, 1H, H-2 or H-3), 0.93 (s, 9H, $SiC(CH_3)_3$), 0.19, 0.17 (2s, 2 × 3H, 2 × $SiCH_3$); FT-IR (film): $\tilde{\nu} = 1697$ (C=O, α,β-unsat. ketone); HR-MS (EI+): calcd for $C_8H_{10}O_3SiI$ $[M-C(CH_3)_3]^+$: 308.944400; found: 308.944857.

(2*R*,3*S*,4*S*)-4-[(tert-Butyldimethylsilyl)oxy]-2,3-epoxy-6-(3-methylbut-3-en-1-ynyl)-5-cyclohexen-1-one (18): $Pd(PPh_3)_2Cl_2$ (0.0092 g, 5 mol%), (3-methylbut-3-en-1-ynyl)tributyltin (0.120 g, 0.34 mmol) and CuI (0.0049 g, 10 mol%) were added to a solution of **17** (0.096 g, 0.26 mmol) in THF (2 mL). After the reaction mixture was stirred at RT for 3 h, 10% aqueous Na_2SO_3 solution (5 mL) was added to the suspension. The mixture was washed with 10% aqueous KF solution (4 mL) and extracted with diethyl ether (3 × 8 mL), the combined organic layers were dried ($MgSO_4$) and the solvent evaporated to give a dark residue. Purification by preparative TLC (AcOEt/hexane 1:9) afforded **18** (0.080 g, 98%) as a colourless oil. $[\alpha]_D^{20} = +148.7$ ($c = 0.15$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$, 300 K, TMS): $\delta =$ 6.85 (dd, $^3J(H,H) = 5.1$ Hz, $^4J(H,H) = 2.7$ Hz, 1H, H-5), 5.44 (s, 1H, C=CH_2), 5.35 (t, 1H, $^3J(H,H) = 1.5$ Hz, C=CH_2), 4.77 (d, $^3J(H,H) =$ 4.5 Hz, 1H, H-4), 3.82–3.79 (m, 1H, H-3), 3.58 (dd, $^3J(H,H) = 3.6$ Hz, $^4J(H,H) = 0.9$ Hz, 1H, H-2), 1.94 (s, 3H, CH_3), 0.92 (s, 9H, $SiC(CH_3)_3$), 0.19, 0.16 (2s, 2 × 3H, 2 × $SiCH_3$); FT-IR (film): $\tilde{\nu} = 1697$ (C=O, α,β-unsat. ketone); HR-MS (EI+): calcd for $C_{17}H_{24}O_3Si$ $[M]^+$: 304.149473; found: 304.148946.

(2*R*,3*S*,4*S*)-2,3-Epoxy-4-hydroxy-6-(3-methylbut-3-en-1-ynyl)-5-cyclohexen-1-one (1): (+)-Harveynone: 40% wt HF in water (0.0072 mL, 0.19 mmol) was added at RT to a solution of **18** (0.045 g, 0.15 mmol) in acetonitrile (1 mL). The reaction mixture was stirred until all starting material had been consumed. Saturated aqueous $NaHCO_3$ solution (2 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 6 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to yield a residue which was purified by preparative TLC (AcOEt/hexane 3:7). (+)-Harveynone **1** (0.026 g, 92%) was obtained as a colourless oil. $[\alpha]_D^{20} = +206.6$ ($c = 0.38$, anhydrous MeOH);[2a] *ent*-**1**: $[\alpha]_D = -208$ ($c = 0.45$, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, 300 K, TMS): $\delta = 6.85$ (dd, $^3J(H,H) = 5.1$ Hz, $^4J(H,H) =$ 2.7 Hz, 1H, H-5), 5.44 (s, 1H, C=CH_2), 5.35 (t, $^3J(H,H) = 1.5$ Hz, 1H, C=CH_2), 4.77 (d, $^3J(H,H) = 4.5$ Hz, 1H, H-4), 3.82–3.79 (m, 1H, H-3), 3.58 (dd, $^3J(H,H) = 3.6$ Hz, $^4J(H,H) = 0.9$ Hz, 1H, H-2), 1.94 (s, 3H, CH_3); FT-IR (film): $\tilde{\nu} = 3469$ (O–H), 1697 (C=O, α,β-unsat. ketone), 1616 (C=C); HR-MS (EI+): calcd for $C_{11}H_{10}O_3$ $[M]^+$: 190.062994; found: 190.063087.

(1*R*,2*R*,3*S*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-6-(3-methylbut-3-en-1-ynyl)-5-cyclohexen-1-ol (19) and (1*S*,2*R*,3*S*,4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-2,3-epoxy-6-(3-methylbut-3-en-1-ynyl)-5-cyclohexen-1-ol (20): $CeCl_3 \cdot 7H_2O$ (0.060 g, 0.16 mmol) and $NaBH_4$ (0.025 g, 0.66 mmol) were added at −78 °C to a solution of **18** (0.050 g, 0.16 mmol) in MeOH (1.5 mL). The reaction mixture was stirred at −78 °C until all the starting material had been consumed. Saturated aqueous NH_4Cl solution (2 mL) was added and the mixture was extracted with diethyl ether (3 × 6 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to yield a mixture of diastereoisomers **19** and **20** (0.050 g, 99%, *dr* 2.7:1) as a colourless oil, which was used in the next step without further purification. Compound **19**: ^{1}H NMR (300 MHz, $CDCl_3$, 300 K, TMS): $\delta = 5.93$ (dd, $^3J(H,H) = 5.1$ Hz, $^4J(H,H) = 1.5$ Hz, 1H, H-5), 5.35 (s, 1H, C=CH_2), 5.30–5.29 (m, 1H, C=CH_2), 4.55 (m, 1H, H-1 or H-4), 4.40 (m, 1H, H-1 or H-4), 3.43 (m, 1H, H-2 or H-3), 3.23 (m, 1H, H-2 or H-3), 1.92 (s, 3H, CH_3), 0.92 (s, 9H, $SiC(CH_3)_3$), 0.15, 0.14 (2s, 2 × 3H, 2 × $SiCH_3$). Compound **20**: ^{1}H NMR (300 MHz, $CDCl_3$, 300 K, TMS): $\delta = 5.89$ (m, 1H, H-5), 5.35 (s, 1H, C=CH_2), 5.29 (m, 1H, C=CH_2), 4.50 (s, 1H, H-1, H-4), 3.58 (t, $^3J(H,H) =$ 3.6 Hz, 1H, H-2 or H-3), 3.37 (m, 1H, H-2 or H-3), 1.93 (s, 3H, CH_3), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.14, 0.13 (2s, 2 × 3H, 2 × $SiCH_3$).

(1*R*,2*R*,3*S*,4*S*)-2,3-Epoxy-6-(3-methylbut-3-en-1-ynyl)-5-cyclohexen-1,4-diol [(−)-asperpentyn (2)] and (1*S*,2*R*,3*S*,4*S*)-2,3-epoxy-6-(3-methylbut-3-en-1-ynyl)-5-cyclohexen-1,4-diol (21): 40% wt HF in water (0.008 mL, 0.20 mmol) was added at RT to a solution of **19** and **20** (0.050 g, 0.16 mmol) in acetonitrile (1.5 mL). The reaction mixture was stirred until all starting material had been consumed. Saturated aqueous $NaHCO_3$ solution (2 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 6 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to yield a residue which was purified by preparative TLC (AcOEt/hexane 5:5). (−)-Asperpentyn **2** (0.023 g, 73%) was obtained as a colourless oil and its diastereoisomer **21** (0.008 g, 27%) was obtained as white crystals. (−)-Asperpentyn (**2**): $[\alpha]_D^{20} = -17.1$ ($c = 0.28$, acetone),[3] $[\alpha]_D^{20} = -20.0$ ($c = 0.1$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$, 300 K, TMS): $\delta = 6.08$ (dd, $^3J(H,H) = 5.1$ Hz, $^4J(H,H) = 1.8$ Hz, 1H, H-5), 5.36 (d, $^3J(H,H) = 0.9$ Hz, 1H, C=CH_2), 5.30 (t, $^3J(H,H) = 1.5$ Hz, 1H, C=CH_2), 4.53 (d, 1H, $^3J(H,H) = 5.7$ Hz, H-1 or H-4), 4.50 (s, 1H, H-1 or H-4), 3.41 (t, $^3J(H,H) = 1.5$ Hz, 1H, H-2 or H-3), 3.35–3.34 (m, 1H, H-2 or H-3), 1.92 (s, 3H, CH_3); ^{13}C NMR (100.61 MHz, $CDCl_3$, 300 K, TMS): $\delta = 131.2$ (C-5), 126.1 (C-6 or C=CH_2), 123.1 (C=CH_2), 122.9 (C-6 or C=CH_2), 92.2 (C≡C), 86.7 (C≡C), 65.5, 62.7 (C-1, C-4), 52.2, 51.4 (C-2, C-3), 23.2 (CH_3); FT-IR (film): $\tilde{\nu} = 3390$, 3320 (O–H); HR-MS (EI+): calcd for $C_{11}H_{11}O_2$ $[M-OH]^+$: 175.075905; found: 175.075970. Compound **21**: $[\alpha]_D^{20} = -12.7$ ($c = 0.41$, acetone); m.p. 132–134 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 300 K, TMS): $\delta = 6.05-6.02$ (m, 1H, H-5), 5.36 (d, 1H, $^3J(H,H) = 0.9$ Hz, C=CH_2), 5.31–5.30 (m, 1H, C=CH_2), 4.54 (d, 1H, $^3J(H,H) = 5.7$ Hz, H-1 or H-4), 4.50 (m, 1H, H-1 or H-4), 3.62–3.59 (m, 1H, H-2 or H-3), 3.51–3.49 (m, 1H, H-2 or H-3), 1.92 (s, 3H, CH_3); FT-IR (KBr): $\tilde{\nu} = 3524$, 3357 (O–H); HR-MS (EI+): calcd for $C_{11}H_{12}O_3$ $[M]^+$: 192.078644; found: 192.078853.

(2*R*,3*S*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-6-methyl-5-cyclohexen-1-one (22): $AsPh_3$ (0.0109 g, 10 mol%), $Pd_2(dba)_3 \cdot CHCl_3$ (0.0095 g, 5 mol% of Pd) and CuI (0.0068 g, 10 mol%) were added to a solution of **17** (0.136 g, 0.37 mmol) in THF (2 mL). The mixture was stirred for 10 min and then Me_4Sn (0.194 g, 1.11 mmol) in THF (0.5 mL) was added. After stirring at 80 °C for 30 h, the suspension was cooled and 10% aqueous Na_2SO_3 solution (5 mL) was added. The mixture was washed with 10% aqueous KF solution (4 mL) and extracted with diethyl ether (3 × 8 mL), the combined organic layers were dried ($MgSO_4$) and the solvent evaporated to give an orange residue. Purification by preparative TLC (AcOEt/hexane 1:9) afforded **22** (0.086 g, 91%) as a colourless oil. $[\alpha]_D^{28} = +251.3$ ($c = 1.40$, anhydrous $CHCl_3$),[10b] $[\alpha]_D^{28} = +250.72$ ($c = 1.17$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 300 K, TMS): $\delta = 6.30-6.27$ (m, 1H, H-5), 4.64 (dd, $^3J(H,H) = 5.7$ Hz, $^3J(H,H) = 1.2$ Hz, 1H, H-4), 3.65–3.62 (m, 1H, H-3), 3.48 (dd, $^3J(H,H) = 3.6$ Hz, $^4J(H,H) = 0.9$ Hz, 1H, H-2), 1.84 (s, 3H, CH_3), 0.92 (s, 9H, $SiC(CH_3)_3$), 0.17, 0.15 (2s, 2 × 3H, 2 × $SiCH_3$); FT-IR (film): $\tilde{\nu} = 1683$ (C=O, α,β-unsat. ketone); HR-MS (EI+): calcd for $C_{12}H_{19}O_3I$ $[M-CH_3]^+$: 239.110348; found: 239.110491.

(2*R*,3*S*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-6-methyl-5-cyclohexen-1-one (22): $AsPh_3$ (0.012 g, 10 mol%), $Pd_2(dba)_3 \cdot CHCl_3$ (0.0105 g,

5 mol % of Pd) were added to a solution of **17** (0.150 g, 0.41 mmol) in THF (2.5 mL). The mixture was stirred for 10 min and then diethylamine (0.129 mL, 1.24 mmol) and Me_4Sn (0.214 g, 1.24 mmol) in THF (0.7 mL) were added. After stirring at 80 °C for 24 h, the suspension was cooled and 10 % aqueous Na_2SO_3 solution (5 mL) was added. The mixture was washed with 10 % aqueous KF solution (5 mL) and extracted with diethyl ether (3×10 mL), the combined organic layers were dried ($MgSO_4$) and the solvent evaporated to give an orange residue. Purification by preparative TLC (AcOEt/hexane 1:9) afforded **22** (0.105 g, quantitative) as a colourless oil. The sprectral data are described in the previous experiment.

(2*R*,3*S*,4*S*)-2,3-Epoxy-4-hydroxy-6-methyl-5-cyclohexen-1-one (3): **(+)-epiepoformin**: 40 % wt HF in water (0.0085 mL, 0.22 mmol) was added at RT to a solution of **22** (0.045 g, 0.18 mmol) in acetonitrile (1 mL). The reaction mixture was stirred until all starting material had been consumed. Saturated aqueous $NaHCO_3$ solution (2 mL) was added and the mixture was extracted with CH_2Cl_2 (3×6 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to yield a residue which was purified by preparative TLC (AcOEt/hexane 3:7). (+)-Epiepoformin (0.025 g, 99 %) was obtained as a colourless oil. $[\alpha]_D^{28} = +314.5$ ($c = 0.49$, EtOH),[5] $[\alpha]_D^{28} = +316.4$ ($c = 0.37$, EtOH); m.p. 84 – 85 °C,[5] m.p. 87.5 – 88.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 300 K, TMS): $\delta = 6.48 - 6.44$ (m, 1H, H-5), 4.67 (d, ^3J(H,H) = 6.0 Hz, 1H, H-4), 3.80 – 3.77 (m, 1H, H-3), 3.52 (dd, ^3J(H,H) = 3.6 Hz, ^4J(H,H) = 1.2 Hz, 1H, H-2), 1.86 (s, 3H, CH_3); FT-IR (film): 3422 (O–H), 1673 (C=O, α,β-unsat. ketone); HR-MS (EI+): calcd for $C_7H_8O_3$ $[M]^+$: 140.047344; found: 140.047123.

(1*R*,2*R*,3*S*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-6-methyl-5-cyclohexen-1-ol (23) and (1*S*,2*R*,3*S*,4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-2,3-epoxy-6-methyl-5-cyclohexen-1-ol (24): $CeCl_3 \cdot 7H_2O$ (0.117 g, 0.32 mmol) was added at RT to a solution of **22** (0.081 g, 0.32 mmol) in MeOH (2.5 mL) and at −78 °C was added $NaBH_4$ (0.048 g, 0.13 mmol). The reaction mixture was stirred at −78 °C until all starting material had been consumed. Saturated aqueous NH_4Cl solution (2 mL) was added and the mixture was extracted with diethyl ether (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to yield a mixture of diastereoisomers **23** and **24** (0.075 g, 92 %) as a colourless oil, which was used in the next step without further purification.

(1*R*,2*R*,3*S*,4*S*)-2,3-Epoxy-6-methyl-5-cyclohexen-1,4-diol [(−)-theobroxide (4)] and (1*S*,2*R*,3*S*,4*S*)-2,3-epoxy-6-methyl-5-cyclohexen-1,4-diol (25): 40 % wt HF in water (0.0094 mL, 0.24 mmol) was added at RT to a solution of **23** and **24** (0.050 g, 0.19 mmol) in acetonitrile (1.5 mL). The reaction mixture was stirred until all starting material had been consumed. Saturated aqueous $NaHCO_3$ solution (2 mL) was added and the mixture was extracted with CH_2Cl_2 (3×8 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to yield a residue which was purified by preparative TLC (AcOEt). (−)-Theobroxide **4** (0.023 g, 84 %) was obtained as a a white solid; the diastereoisomer **25** (0.005 g, 15 %) was obtained as a colourless oil. (−)-Theobroxide **4**: $[\alpha]_D^{28} = -6.18$ ($c = 0.35$, EtOH),[5] $[\alpha]_D^{28} = -6.25$ ($c = 0.40$, EtOH); m.p. 98 – 99 °C,[5] m.p. 101 – 102 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K, TMS): $\delta = 5.53 - 5.51$ (m, 1H, H-5), 4.46 (br s, 1H, H-1 or H-4), 4.25 (s, 1H, H-1 or H-4), 3.37 – 3.36 (m, 1H, H-2 or H-3), 3.30 (m, 1H, H-2 or H-3), 3.15 (br s, 2H, $2 \times OH$), 1.83 (s, 3H, CH_3); ^{13}C NMR (100.61 MHz, $CDCl_3$, 300 K, TMS): $\delta = 135.1$ (C-6), 121.5 (C-5), 66.2, 63.0 (C-1, C-4), 52.9, 51.8 (C-2, C-3), 21.1 (CH_3); FT-IR (film): $\tilde{\nu} = 3366$ (O–H); HR-MS (EI+): calcd for $C_7H_{10}O_3$ $[M]^+$: 142.062994; found: 142.062493. Compound **25**: $[\alpha]_D^{28} = +48.57$ ($c = 0.35$, EtOH),[5] $[\alpha]_D^{28} = +47.52$ ($c = 0.59$, EtOH); m.p. 94 – 96 °C,[5] m.p. 97 – 99 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 300 K, TMS): $\delta = 5.49$ (m, 1H, H-5), 4.41 (m, 1H, H-1 or H-4),4.30 (br s, 1H, H-1 or H-4), 3.56 – 3.54 (m, 1H, H-2 or H-3), 3.52 – 3.49 (m, 1H, H-2 or H-3), 2.23 (br s, 2H, $2 \times OH$), 1.84 (s, 3H, CH_3); HR-MS (EI+): calcd for $C_7H_{10}O_3$ $[M]^+$: 142.062994; found: 142.063110.

(2*R*,3*S*,4*S*)-4-Hydroxy-2,3-epoxy-6-iodo-5-cyclohexen-1-one (26): **(+)-iodoxone**: 40 % wt HF in water (0.0039 mL, 0.102 mmol) was added at RT to a solution of **17** (0.030 g, 0.082 mmol) in acetonitrile (1 mL). The reaction mixture was stirred until all starting material had been consumed. Saturated aqueous $NaHCO_3$ solution (2 mL) was added and the mixture was extracted with CH_2Cl_2 (3×6 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to yield a residue, which after purification by preparative TLC (AcOEt/hexane 3:7) afforded (+)-iodoxone **26** (0.020 g, 99 %) as a colourless oil. $[\alpha]_D^{20} = +94.8$ ($c = 0.61$, anhydrous acetone),[2a] $[\alpha]_D = +96.1$ ($c = 0.95$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$, 300 K, TMS): $\delta = 7.46$ (dd, ^3J(H,H) = 5.1 Hz, ^4J(H,H) = 2.7 Hz, 1H, H-5), 4.64 (d, ^3J(H,H) = 3.0 Hz, 1H, H-4),; 3.85 – 3.83 (m, 1H, H-2 or H-3), 3.67 – 3.65 (m, 1H, H-2 or H-3); FT-IR (KBr): $\tilde{\nu} = 3360$ (O–H), 1678 (C=O, α,β-unsat. ketone), 1594 (C=C); HR-MS (EI+): calcd for $C_6H_5O_3I$ $[M]^+$: 251.928346; found: 251.928039.

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