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Enantioselective Synthesis of Natural Polyoxygenated Cyclohexanes and Cyclohexenes from [(*p*-Tolylsulfinyl)methyl]-*p*-quinols

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Abstract: Exploitation of the β-hydroxysulfoxide fragment present in a number of enantiomerically pure (S*R*)- and (S*S*)-[(*p*-tolylsulfinyl)methyl]-*p*-quinols allowed chemo- and stereocontrolled conjugate additions of different organoaluminium reagents to the cyclohexadienone moiety. The same fragment was also shown to act as an efficient chiral masking carbonyl group, after oxidation to sulfone and retroaddition in basic medium, with elimination of methyl *p*-tolyl sulfone. Through the use of both transformations as key steps, enantiocontrolled syntheses of different natural products—such as the two enantiomers of dihydroepiepoformin, (−)-gabosine O, (+)-epiepoformin, (−)-theobroxide and (+)-4-epigabosine A (an epimer of the natural product gabosine A)—has been achieved. The presence of the β-hydroxy sulfone moiety makes the cyclic structures rigid, allowing a number of stereoselective transformations such as carbonyl reductions, enone epoxidations or *cis*-dihydroxylations, en route to the natural structures. The observed selectivities were dependent on the particular substitution in each substrate, providing evidence of a strong influence of remote groups on the preferred approach of the reactants to the reactive conformations. An advanced precursor of natural (+)-harveynone was also synthesized, but the isolation of the natural product was not possible because of the instability of the corresponding enone, containing a triple bond, under the basic conditions necessary to eliminate the β-hydroxy sulfone. This demonstrated that the limitations of the use of the β-hydroxy sulfoxide as a chiral protecting carbonyl group were dependent on the relative stabilities of the final targets in the presence of the required base.

Keywords: asymmetric synthesis · cyclohexanes · cyclohexenes · natural products · quinols

Introduction

Stereoselective approaches to polyhydroxy-substituted cyclohexanes and cyclohexenes continue to attract considerable attention, due to the widespread appearance of these structural motifs in natural products such as cyclitols,[1] carbasugars[1b,2] or alkaloids.[3] The cyclohexene oxide moiety[4] is also a recurring structural feature found in a number of natural derivatives. The stereocontrolled transformation of cyclohexanones and cyclohexenones is a general means of access to this important type of compounds, while conversion of the ketone function into a chiral masked group is a common strategy allowing further stereoselective introduction of appropriate substitution en route to natural products. This goal has been successfully achieved through the conversion of the cyclohexanone carbonyl group into chiral acetal[5] or hydrazone moieties.[6] Enantiopure α-acetoxysulfones, introduced by Trost[7] as chiral aldehyde equivalents, have mainly been used in acyclic systems. Organocatalysis,[8] as a strategy to transform ketones into intermediate enantiopure imines or enamines, is nowadays often successfully applied to achieve this goal. In spite of the important advances already achieved, efficient asymmetric syntheses require new chiral carbonyl equivalents to enable improved stereoselective transformations.

In connection with a project geared towards extending the applications of sulfoxides in asymmetric synthesis,[9] we have found that a β-hydroxy sulfoxide moiety placed at C4 in a system such as 4-[(*p*-tolylsulfinyl)methyl]cyclohexa-2,5-dienone (**1**, R^1 = H; Scheme 1), can be regarded as a chiral ketone equivalent:[10] after stereoselective transformations of the ring to afford intermediates such as **2** and **3**, a carbon-

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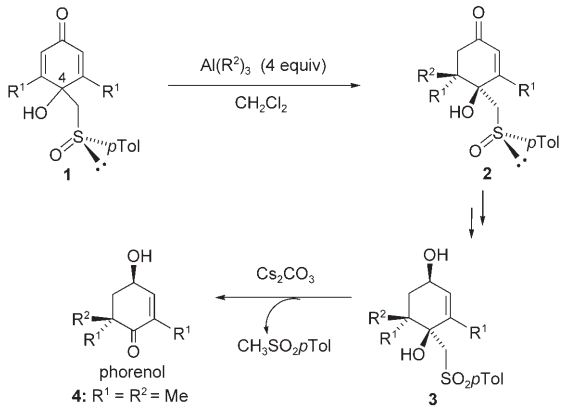
yl group at C4 can be recovered through oxidation of the sulfoxide to a sulfone and basic retroaddition with elimination of methyl *p*-tolyl sulfone, as shown in the transformation of **3** into **4**. A systematic study on the behaviour of **1** as an enantiopure conjugate acceptor[11] revealed that the methylsulfinyl substituent permitted differentiation between the two diastereotopic faces of the double bonds, directing conjugate additions of organoaluminium reagents from the face containing the OH group in a highly diastereoselective way and with efficient desymmetrization of the cyclohexadienone moiety (Scheme 1).

The interest in using *p*-quinols **1** as starting materials for chiral targets is based on the combination of asymmetric Michael-type additions, affording **2**, and subsequent stereoselective transformation processes on the resulting cyclohexenones, completed with oxidation to the sulfones and elimination of $MeSO_2pTol$ to reestablish the C4 carbonyl group. This approach has previously allowed us to synthesize different chiral, nonracemic alkyl hydroxy cyclohexenones such as phorenol (**4**).[10]

We have also applied this methodology to the synthesis of an enantiopure 3,6-dihydroxy-5-methyl-1-vinylcyclohexene derivative, Diels–Alder reactions of which with 5-methoxy-2- or 3-(*p*-tolylsulfinyl)-1,4-naphthoquinone resulted in the totally enantio- and regioselective syntheses of the angucyclinone-type antibiotics rubiginone A_2 and C_2 and their 11-methoxy regioisomers.[12]



Scheme 1. Key steps in the synthesis of enantiopure cyclohexenones from [*p*-(tolylsulfinyl)methyl]-*p*-quinols **1**.

As a number of polyhydroxy-substituted cyclohexanes and cyclohexenes, together with their epoxide analogues, are found in many natural products and have also been prepared for use as intermediates in total synthesis, we decided to extend our methodology to the synthesis of different polyoxygenated cyclohexane and cyclohexene derivatives. Stereocontrolled transformation of the cyclic systems could open easy access to a variety of natural structures. We first focused on natural products containing cyclohexane structural elements, such as the two enantiomers of dihydroepiepoformin (**5**)[13] and (−)-gabosine O (**6**) (Figure 1) and then

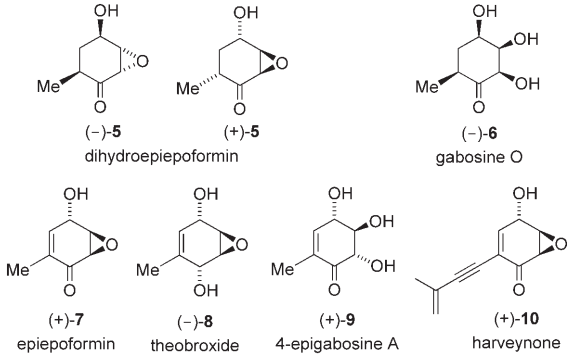


Figure 1. Structures of natural polyoxygenated cyclohexane and cyclohexene derivatives.

turned our attention to cyclohexene derivatives such as (+)-epiepoformin (**7**),[13] (−)-theobroxide (**8**), (+)-4-epigabosine A (**9**; an epimer of the natural product gabosine A) and (+)-harveynone (**10**).

Dihydroepiepoformin (**5**) was isolated in 1995 by Kuo et al.[14] by fermentation of *Penicillium patulum* and was found to have antagonistic activity for interleukin-1, though the authors did not report the specific rotation of the isolat-

Abstract in Spanish: *El fragmento de β-hidroxisulfóxido presente en varios (S*R*)- y (S*S*)-[(*p*-tolilsulfinil)metil]-*p*-quinoles enantioméricamente puros ha permitido la adición conjugada quimio- y estereocontrolada de diferentes reactivos organoalumínicos sobre la unidad de ciclohexadienona. El mismo fragmento ha demostrado actuar como un grupo carbonilo quiral enmascarado muy eficiente, tras oxidación a sulfona y eliminación en medio básico de metil p-tolil sulfona. Usando ambas transformaciones como etapas clave, se ha logrado la síntesis enantiocontrolada de diferentes productos naturales como la dihidroepiepoformina, (−)-gabosina O, (+)-epiepoformina, (−)-theobroxido y (+)-4-epigabosina A, epímero del producto natural gabosina A. La presencia del fragmento de β-hidroxi sulfona confiere rigidez a las estructuras cíclicas lo que permite llevar a cabo un gran número de transformaciones estereoselectivas como reducciones de grupos carbonilo, epoxidaciones de enonas o dihidroxilaciones* cis*, en ruta hacia los productos naturales. Las selectividades observadas dependen de la sustitución particular de cada sustrato, evidenciándose una fuerte influencia de grupos remotos en las aproximaciones preferidas de los reactantes sobre las correspondientes conformaciones más reactivas. También se ha podido sintetizar un precursor avanzado de la (+)-harveynona, pero el aislamiento de este producto natural no fue posible debido a la inestabilidad de la correspondiente enona, portando un triple enlace, en las condiciones básicas necesarias para eliminar el fragmento de β-hidroxi sulfona. Este resultado pone en evidencia las limitaciones de usar el fragmento de β-hidroxi sulfóxido como un grupo protector quiral de carbonilos que va a depender de la estabilidad relativa del compuesto final en presencia de la base requerida.*

ed compound or its absolute configuration. In our previous communication,[13] we described the independent syntheses of both enantiomers of this natural product and determined their absolute configurations.

The carbasugar (−)-gabosine O (**6**) was isolated from different *Streptomyces* strains[15,16] and showed weak DNA-binding properties.[16] Its absolute configuration has recently been assigned by Figueredo et al.,[17] through an enantioselective total synthesis using an enzymatically resolved protected cyclohexenone as starting material.

(+)-Epiepoformin (**7**) was isolated in 1978 by Nagasawa[18] from the culture filtrate of an unidentified fungus separated from a diseased leaf, and showed marked inhibition activity against the germination of lettuce seeds. The natural enantiomer has been synthesized by several authors using different strategies: Ogasawara et al.[19] based their approach on a retro-Diels–Alder reaction to recover the cyclohexenone fragment from a stereoselectively functionalized quinone Diels–Alder adduct, previously asymmetrized by isomerization with an enantiopure BINAP–Rh^I catalyst,[20] while the formation of a bicyclic adduct in a cinchonine-catalysed reaction between 3-hydroxy-2-pyrone and an acrylamide derived from a chiral oxazolidinone was the key step in the approach of Okamura et al.[21] (−)-Quinic acid was the starting material in the synthesis reported in 2000 by Maycock et al.,[22], whereas a chiral building block obtained by enzymatic reduction was used by Kitahara et al.[23] to synthesize (+)-**7** in 2003.

(−)-Theobroxide (**8**), isolated from the culture filtrate of the fungus *Lasiodiplodia theobromae*,[24] is a potato microtuber inducing substance. Ogasawara[19] and Maycock[22] synthesized both enantiomers of **8** and the natural one, respectively, by applying the strategies described above, while Arimoto[25] recently published an enantioselective synthesis of (−)-**8** based on photooxygenation of 1-methyl-1,4-cyclohexadiene and enzymatic resolution of an immediate precursor.

(+)-4-Epigabosine A (**9**), the epimer of the natural product (−)-gabosine A,[15] had not been synthesized to date.

All these compounds **7**–**9** share the feature of a methyl substituent situated on the cyclohexene skeleton. Another target in our work has been (+)-harveynone (**10**) (Figure 1), containing an enyne substituent on the cyclohexene system. This natural product was isolated from the tea gray fungus *Pestalotiopsis theae* and is a phytotoxin.[26] Maycock[22] has also synthesized (+)-**10** from (−)-quinic acid. Other syntheses of harveynone in enantiopure form have been reported by Ogasawara,[27] Johnson[28] and Negishi[29], together with one of the racemate by Taylor,[30] based on the use of a Pd-catalysed cross-coupling reaction to introduce the acetylenic substituent onto a functionalized α-iodocyclohexenone.

We now report new asymmetric total syntheses of (−)-gabosine O (**6**), (−)-theobroxide (**8**) and (+)-4-epigabosine A (**9**), as well as an enantioselective approach to an advanced precursor of (+)-harveynone (**10**). All are based on the combination of the stereoselective and chemoselective introduction of a methyl or alkynyl group onto a *p*-quinol **1** from an organoaluminium derivative, stereoselective transformations on the resulting enantiopure cyclohexenone, and retro-addition of methyl *p*-tolylsulfone, to reestablish the carbonyl group at C4. We also report full details of the methodology used for the preparation of all synthetic intermediates en route to the two enantiomers of dihydroepiepoformin (**5**) and to (+)-epiepoformin (**7**).[13] All this work has allowed us to establish advantages and limitations of using the β-hydroxy sulfoxide moiety as a chiral masking carbonyl group in a cyclic system.

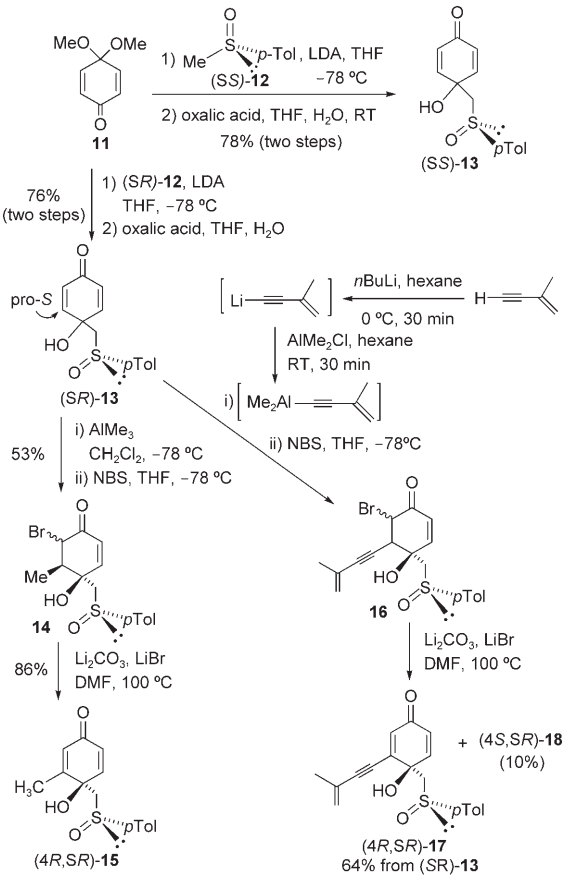
Results and Discussion

The enantiomerically pure 4-hydroxy-4-[(*p*-tolylsulfinyl)methyl]cyclohexa-2,5-dienones (S*R*)-**13**[31] and (S*S*)-**13** (Scheme 2)[12] necessary to synthesize the two enantiomers of dihydroepiepoformin (**5**) and (+)-gabosine O (**6**) were obtained, as reported previously, by treatment of the lithium anions derived from (S*R*)-[32] or (S*S*)-methyl *p*-tolyl sulfoxide (**12**) with *p*-benzoquinone dimethyl monoketal (**11**),[33] followed by hydrolysis of the intermediate acetal with oxalic acid, in 76 and 78% overall yields, respectively.

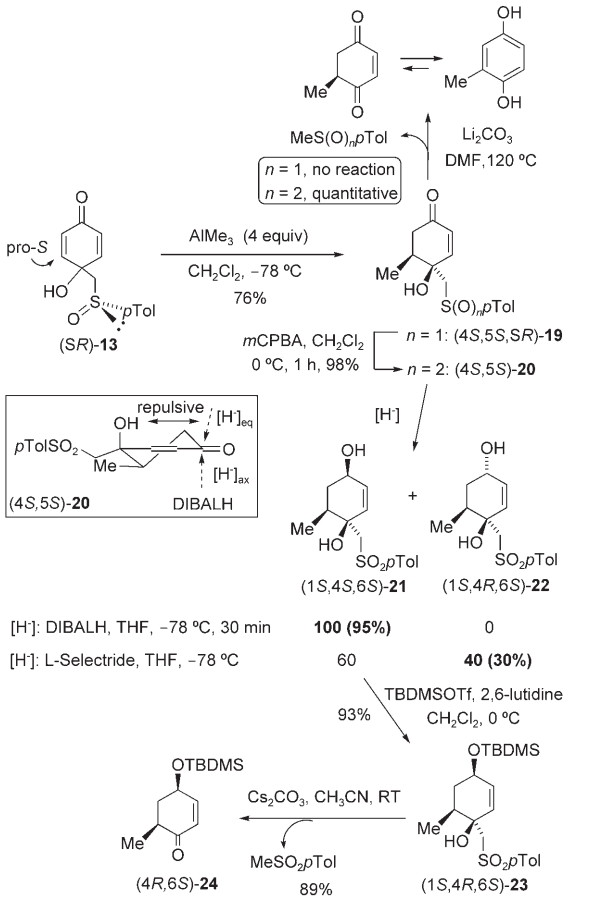
The synthesis of the asymmetrically substituted 4-hydroxy-3-methyl-4-[(*p*-tolylsulfinyl)methyl]cyclohexa-2,5-dienone (4*R*,S*R*)-**15**[11b] was achieved from *p*-quinol (S*R*)-**13** in a two-pot, three-step sequence based on the 1,4-addition of $AlMe_3$[34] and trapping of the intermediate aluminium enolate with *N*-bromosuccinimide (NBS), followed by HBr elimination upon heating of the resulting mixture of epimeric bromides **14** with Li_2CO_3/LiBr (Scheme 2). The addition of $AlMe_3$ to (S*R*)-**13** occurred exclusively at the pro-*S* conjugate position.

In a similar reaction sequence, starting from the *p*-quinol (S*R*)-**13**, the 4-hydroxy-3-(3-methylbut-3-en-1-ynyl)-4-[(*p*-tolylsulfinyl)methyl]cyclohexa-2,5-dienone isomer (4*R*,S*R*)-**17** could be synthesized as shown in Scheme 2. In this case, the necessary dimethyl[3-methylbut-3-en-1-yl]aluminium reagent was generated from commercially available 3-methylbut-3-en-1-yne by sequential treatment with *n*BuLi at 0°C and with $AlMe_2Cl$ at room temperature. After dilution with CH_2Cl_2, the *p*-quinol (S*R*)-**13** was added to the resulting mixture. The order of addition of the reagents was essential to achieve successful selective 1,4-conjugate addition at the pro-*S* position.[35] Once the reaction was complete, the intermediate enolate was quenched with NBS at −78°C. The resulting mixture of C6 bromo epimers **16** was treated with Li_2CO_3 and LiBr to afford a mixture of *p*-quinols (4*R*,S*R*)-**17** and (4*S*,S*R*)-**18** that could be isolated pure, after flash chromatography, in 64 and 10% yields, respectively. The mixture of epimers must reflect the formation of a similar mixture of diastereomers in the alkynyl aluminium reagent addition step.

With the starting *p*-quinols to hand, we next focused on the stereoselective transformations of the cyclohexadienone rings, en route to the natural products. Taking into account the known chemo- and diastereoselective addition of $AlMe_3$ to the (S*R*)- and (S*S*)-*p*-quinols **13**, which occur at the pro-



Scheme 2. Synthesis of *p*-quinols (S*R*)- and (S*S*)-**13**, (4*R*,S*R*)-**15** and (4*R*,S*R*)-**17**.



Scheme 3. Synthesis of the advanced key intermediate (4*R*,6*S*)-**24** from *p*-quinol (S*R*)-**13**.

S[11] and the pro-*R*[12] conjugate positions, respectively, we started the synthesis of the (6*S*)-6-methyl-substituted cyclohexanone rings of natural products (−)-**5** and (−)-**6** (Figure 1) from *p*-quinol (S*R*)-**13**. Treatment of (S*R*)-**13** with 4 equivalents of AlM_3, thus resulted in the chemo- and diastereoselective exclusive formation of (4*S*,5*S*,S*R*)-**19**[11b,34] (Scheme 3), the product of addition at the pro-*S* conjugate position of (S*R*)-**13**, in 76% yield.

In order to check the viability of transforming the β-hydroxy sulfoxide into a carbonyl group, we treated compound **19** with different bases. The retroaddition process to eliminate methyl *p*-tolyl sulfoxide from **19** should be favoured, since the 1,4-diketone that would be formed from the cyclohexenone moiety is a tautomer of 2-methylhydroquinone (Scheme 3). Nevertheless, in spite of the stability of this product, no elimination occurred in the sulfoxide **19**, even when this compound was heated in DMF at 120°C in the presence of Li_2CO_3. We thus decided to improve the leaving group ability by transforming the sulfoxide **19** into the sulfone (4*S*,5*S*)-**20** (*meta*-chloroperbenzoic acid (*m*CPBA), 98%). Upon treatment of **20** with different bases (Li_2CO_3, LiHMDS, Cs_2CO_3) at different temperatures, we indeed observed the quantitative elimination of methyl *p*-tolyl sulfone. Although the hydroquinone was not isolated, the formation of $MeSO_2pTol$ demonstrated the viability of the recovery of the carbonyl moiety.

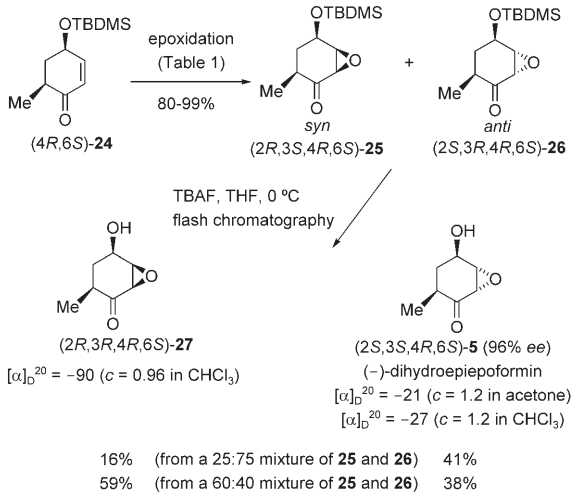
With a view towards functionalization of the cyclic system, we tried to effect the stereoselective reduction of the carbonyl group of **20** before the elimination step. The preferred mode of attack of small hydrides on rigid cyclohexanones is normally axial, and this preference is known to be even higher in cyclohexenones.[36] In compound **20**, a cyclohexenone with a fixed conformation positioning the CH_2SO_2pTol and CH_3 groups in pseudoequatorial orientations, the small hydride DIBALH reacted, as expected, to give rise to the exclusive formation of carbinol (1*S*,4*R*,6*S*)-**21**, resulting from axial attack, which could be isolated in 95% yield (Scheme 3). This excellent stereoselectivity could also be due to the presence of the pseudoaxial OH at C4 in compound **20**, influencing the stereochemical course of hydride approach by obstructing access from the same side through electrostatic interactions[37] and thus enhancing the axial attack preference. The bulky hydride L-Selectride, which should normally promote equatorial attack, did not invert the stereoselectivity of the process in this case, although it was changed to a 40:60 mixture of carbinol epimers (1*S*,4*R*,6*S*)-**21** and (1*S*,4*S*,6*S*)-**22**. Although the minor diastereomer **22** could be isolated by chromatography, the

low (30%) yield prevented its use in the synthesis of other natural targets. Again, the axial OH at C4 of **20**, through repulsive electrostatic interactions,[38] was hindering the otherwise favoured equatorial attack by L-Selectride.

The retroaddition process to eliminate $MeSO_2pTol$ was also tried on derivative **21**, and although we observed the formation of $MeSO_2pTol$ upon basic treatment we were unable to isolate the resulting hydroxycyclohexenone. We next protected the secondary OH in **21** (TBDMSOTf, 2,6-lutidine, 93%), obtaining compound (1*S*,4*R*,6*S*)-**23**. The bulky protecting group was chosen to facilitate the *anti* epoxidation that would be necessary in the next steps to establish the correct stereochemistry of the final target **5**. After treatment of **23** with Cs_2CO_3 in CH_3CN at room temperature, we were able to recover the cyclohexenone (4*R*,6*S*)-**24** in 89% yield.

The epoxidation of the TBDMS-protected carbinol **24** was carried out with different reagents under different conditions (Scheme 4, Table 1) in a search for the best *anti* diastereoselectiviy. As can be seen, use of H_2O_2 (30% aqueous solution) as the oxidant and benzyltrimethylammonium hydroxide (Triton B, 40% in MeOH)[39] as the base in THF at −78°C resulted in a 55:45 mixture of the diastereoisomeric epoxides *syn*-(2*R*,3*S*,4*R*,6*S*)-**25** and *anti*-(2*S*,3*R*,4*R*,6*S*)-**26** (entry 1). Methyl(trifluoromethyl)dioxirane,[40] generated in situ from trifluoroacetone and Oxone and known to be more reactive than dimethyldioxirane, behaved in a similar way, giving rise to a 65:35 mixture of *syn*-**25** and *anti*-**26** (entry 2). Changing the oxidant to the bulkier *tert*-butyl hydroperoxide (TBHP) in the presence of Triton B[41] resulted in a slight inversion of the *syn*-**25**/*anti*-**26** ratio to 40:60 (entry 3). The effect of the temperature was shown to be important, as when the above reaction was carried out at 0°C, a slight but significant excess of the diastereomer *syn*-**25** was once again formed (60:40 mixture of *syn*-**25** and *anti*-**26**, entry 4). Use of the even bulkier triphenylmethyl (trityl) hydroperoxide (Ph_3COOH) in the presence of Triton B[42] at 0°C also gave rise to diastereomer *syn*-**25** as the major component (entry 5). The effect of the temperature was also critical in this case and, after laborious experimentation, we were able to establish that use of Ph_3COOH and Triton B at −78°C and allowing the mixture to reach −30°C until completion resulted in the quantitative formation of a 25:75 mixture of *syn*-**25** and *anti*-**26** (entry 6).

Although the diastereomers **25** and **26** could not be separated at this stage, after removal of the OTBDMS groups (TBAF, THF, 0°C) from the 25:75 mixture the corresponding alcohols, (2*R*,3*R*,4*R*,6*S*)-**27** {$[\alpha]_D^{20} = -90$ ($c = 0.96$ in $CHCl_3$)} and (2*S*,3*S*,4*R*,6*S*)-**5** {$[\alpha]_D^{20} = -21$ ($c = 1.2$ in acetone) or $[\alpha]_D^{20} = -27$ ($c = 1.2$ in $CHCl_3$)}, were isolated by chromatography in 16 and 41% yields, respectively (Scheme 4). When a 60:40 mixture of derivatives **25** and **26** was deprotected, (−)-**27** and (−)-**5** were isolated in 59 and 38% yields, respectively. The spectral parameters of synthetic (−)-**5** (96% *ee*),[43] with the (2*S*,3*S*,4*R*,6*S*) absolute configuration, were identical to those reported for natural dihydroepiepoformin isolated by Kuo.[14]



Scheme 4. Epoxidation of cyclohexenone (4*R*,6*S*)-**24** and completion of the synthesis of (−)-**27** and (−)-dihydroepiepoformin (**5**).

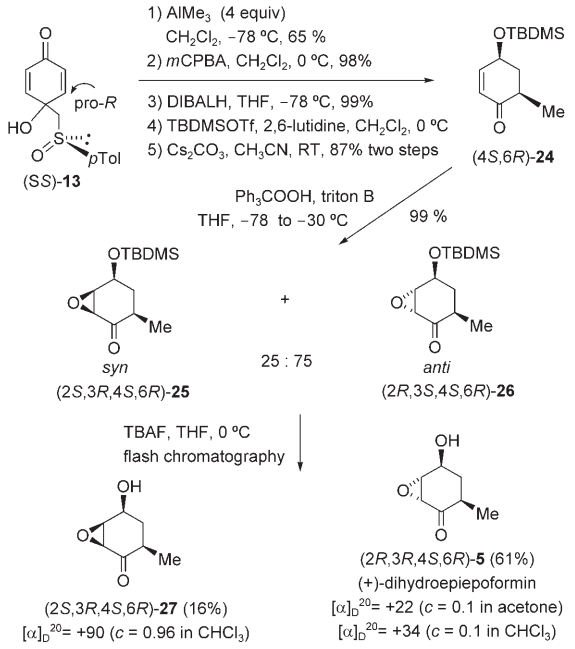
Table 1. Epoxidation of cyclohexenone (4*R*,6*S*)-**24** under different experimental conditions.

Entry	Reagent	Solvent	*T* [°C]	*syn*-**25**	*anti*-**26**
1	H_2O_2,[a] Triton B[b]	THF	−78	55	45
2	Oxone, CF_3COCH_3, $NaHCO_3$	CH_3CN/H_2O	0	65	35
3	TBHP, Triton B[b]	THF	−78	40	60
4	TBHP, Triton B[b]	THF	0	60	40
5	Ph_3CO_2H, Triton B[b]	MeOH	0	60	40
6	Ph_3CO_2H, Triton B[b]	MeOH	−78→−30	25	75

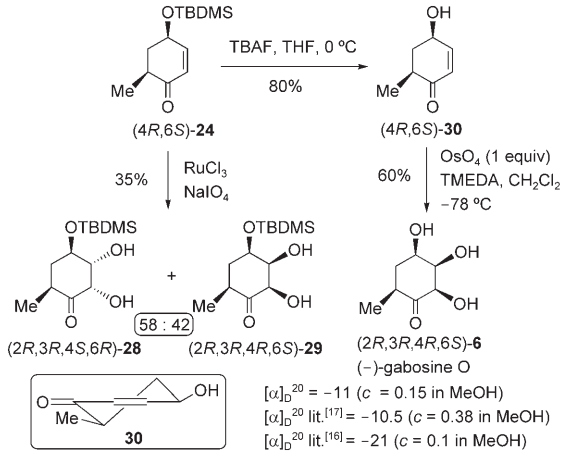
[a] 30% Aqueous solution. [b] 40% Solution in MeOH.

The corresponding enantiomers (+)-**27** and (+)-**5** were readily accessible from *p*-quinol (S*S*)-**13** by a similar sequence of reactions, as summarized in Scheme 5. Initial addition of $AlMe_3$ to (S*S*)-**13** occurred stereo- and chemoselectively at the pro-*R* conjugate position, in a 65% yield. *m*CPBA oxidation of the sulfoxide to the sulfone (98%) was followed by stereoselective DIBALH reduction (99%), secondary OH protection and elimination of $MeSO_2pTol$ (Cs_2CO_3, 87% for the two steps) to give the cyclohexenone (4*S*,6*R*)-**24**,[12] while epoxidation under the conditions described above (Ph_3COOH, Triton B, −78 to −30°C) afforded a 25:75 mixture of (2*S*,3*R*,4*S*,6*R*)-**25** and (2*R*,3*S*,4*S*,6*R*)-**26** in almost quantitative yield (Scheme 5). After desilylation (TBAF) and chromatographic separation, a 16% yield of (2*S*,3*S*,4*S*,6*R*)-**27** {$[\alpha]_D^{20} = +90$ ($c = 0.96$ in $CHCl_3$)} and a 61% yield of (+)-dihydroepiepoformin (2*R*,3*R*,4*S*,6*R*)-**5** (96% *ee*)[43] {$[\alpha]_D^{20} = +22$ ($c = 0.1$ in acetone) or $[\alpha]_D^{20} = +34$ ($c = 0.1$ in $CHCl_3$)} were obtained.

The synthesis of the other natural target bearing a cyclohexane structure—(−)-gabosine O (**6**)—only required the diastereoselective *cis*-dihydroxylation of the double bond of cyclohexenone (4*R*,6*S*)-**24** and deprotection of the alcohol (Scheme 6). When (4*R*,6*S*)-**24** was treated with $RuCl_3$/$NaIO_4$,[44] however, an inseparable 58:42 mixture of diaste-



Scheme 5. Synthesis of (+)-**27** and (+)-dihydroepiepoformin (**5**).



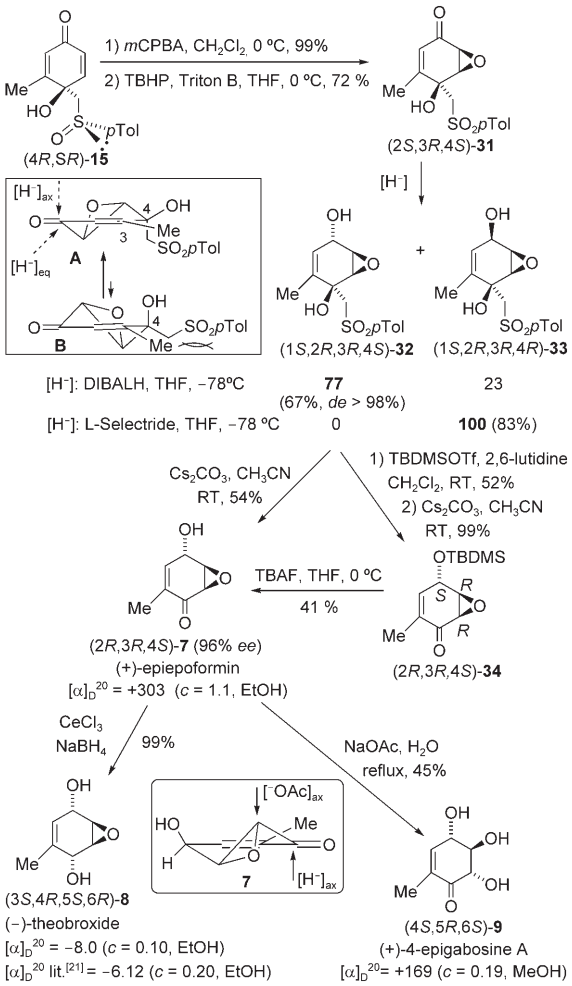
Scheme 6. Synthesis of (−)-gabosine O (**6**) from (4*R*,6*S*)-**24**.

reomeric diols (2*R*,3*R*,4*S*,6*R*)-**28** and (2*S*,3*R*,4*R*,6*S*)-**29** was isolated after flash chromatography in a moderate 35% yield, while OsO_4 dihydroxylation of (4*R*,6*S*)-**24** under different catalytic and stoichiometric conditions only yielded decomposition, aromatic products or poor yields of mixtures of diastereomers **28** and **29**.

The π-facial diastereoselectivities of OsO_4 dihydroxylations are normally governed by steric factors,[17,45] and the bulky OTBDMS protecting group in **24** was slightly favouring dihydroxylation *anti* to the vicinal OTBDMS substituent. On the other hand, the diastereoselectivity of OsO_4 dihydroxylation of free allylic cyclohexenols has been shown to be dependent on the reactive conformation and the possibility of hydrogen bonding. According to Donohoe,[46] diastereoselective attack *anti* to the OH group is normally achieved under standard conditions [OsO_4 (cat), NMO as reoxidant, acetone, H_2O], whereas low selectivity results when hydrogen bonding is able to direct the reagent approach *syn* to the OH (OsO_4, CH_2Cl_2). The relative amount of OsO_4 has also been shown to play an important role. In our case, dihydroxylation of the free carbinol (4*R*,6*S*)-**30**, obtained from **24** by TBAF treatment (80%), confirmed these observations, with the all-*cis* triol (2*R*,3*R*,4*R*,6*R*)-**6**—(−)-gabosine O, with the required stereochemistry—being obtained from cyclohexenone **30** through the use of stoichiometric amounts of OsO_4 under the conditions indicated in Scheme 6. It appears likely that the locked conformation of **30** shown in Scheme 6, with both the OH and methyl substituents in pseudoequatorial dispositions, should be the reactive one. In this case, the efficiency of the hydrogen bonding in directing the *syn* approach of the oxidant to give the *cis*-dihydroxylation product was very high. Both the spectroscopic parameters and the sign of the specific rotation {$[\alpha]_D^{20}$ = −11.0 (*c* = 0.15 in MeOH)} of the final product (2*R*,3*R*,4*R*,6*R*)-**6** were identical to those reported for the natural[16] and synthetic[17] (−)-gabosine O, thus confirming the absolute configurations of all stereogenic centres created from the initial presence of the sulfoxide in the starting *p*-quinol (S*R*)-**13**.

The synthesis of the natural product (+)-epiepoformin (**7**), with a cyclohexene structure, was addressed by starting from *p*-quinol (4*R*,S*R*)-**15** (Scheme 7). Oxidation of **15** (*m*CPBA, 99%) to the corresponding sulfone, followed by TBHP/Triton B epoxidation, which occurred stereoselectively at the more electrophilic unsubstituted double bond, afforded the epoxide (2*S*,3*R*,4*S*)-**31** in 72% yield. The directing effect of the free OH[47] at C4, as well as the preference for approach of the oxidant from the less hindered face of the double bond, *anti* to the CH_2SO_2pTol substituent, must be the origin of the highly diastereoselective formation of compound **31**.

In contrast, the reduction of the carbonyl group in **31** was less stereoselective. We tried different reducing agents, achieving the best results (in terms of yield of the desired diastereomer **32**) by treatment with DIBALH in THF at −78 °C. Under these conditions, the quantitative formation of a 77:23 mixture of epimeric carbinols (1*S*,2*R*,3*R*,4*S*)-**32** and (1*S*,2*R*,3*R*,4*R*)-**33** was observed, from which compound **32** could be separated diastereomerically pure by flash chromatography, in 67% yield. Several factors can influence the stereoselectivity of the reduction of **31**. The preference of DIBALH for the axial approach to the cyclohexenone,[37] would give a different epimer depending on the reactive conformer. The most stable, and probably more reactive, conformation of **31** would be **A** (inset in Scheme 7), in which the severe interaction present in **B** between the Me group at C3 and the pseudoequatorial (*p*-tolylsulfonyl)methyl substituent at C4 is avoided. Axial attack of the small hydride DIBALH on **A** would explain the predominant formation of the (4*S*)-epimer carbinol **32**. Nevertheless, the electrostatic effect of the C4 hydroxy substituent discussed above must decrease this preference. The exclusive formation of epimer (1*S*,2*R*,3*R*,4*R*)-**33** (83% isolated yield) on use



Scheme 7. Syntheses of (+)-epiepoformin (**7**), (−)-theobroxide (**8**) and (+)-4-epigabosine A (**9**).

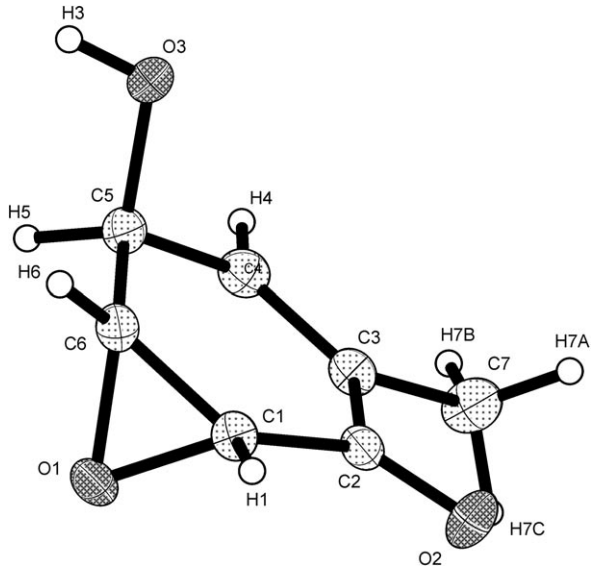


Figure 2. X-ray structure of **7**.

of the bulky hydride L-Selectride, preferring the equatorial approach, is in this case favoured by the repulsive effect of the OH at C4 situated on the opposite face of the reactive conformer **A** (Scheme 7).

The synthesis of (+)-epiepoformin (**7**) was completed after protection of the secondary OH of **32** as a TBDMS ether (52%), elimination of $MeSO_2pTol$ (Cs_2CO_3, 99%), affording (2*R*,3*R*,4*S*)-**34**, and desilylation (TBAF, 41%). The overall yield of these three last steps was only 21%, but a better yield was achieved by direct treatment of carbinol **32** with Cs_2CO_3, which afforded a 54% yield of (2*R*,3*R*,4*S*)-(**7**) {$[\alpha]_D^{20} = +303$ (c = 1.1 in EtOH)}. The optical and spectroscopic properties of synthetic (+)-**7** matched those reported for natural (+)-epiepoformin[18] and its enantiomeric purity was shown to be 96% *ee* after ^{1}H NMR analysis (500 MHz) of the Mosher's esters.[48] The relative configurations of all stereogenic centres in **7** were confirmed by X-ray diffraction (Figure 2).[49]

The transformation of (+)-epiepoformin (**7**) into the other natural target, (−)-theobroxide (**8**), was achieved by treatment with $NaBH_4$ in the presence of $CeCl_3$ (Luche's reagent).[50] Under these conditions the reduction of the carbonyl group of **7** took place quantitatively giving rise, in a highly diastereoselective manner, to the epoxy diol (1*S*,2*R*,3*S*,4*R*)-(**8**) {$[\alpha]_D^{20} = -8.0$ (c = 0.10 in EtOH)}, the product of axial attack of the hydride on cyclohexenone **7** (Scheme 7).[51] The spectroscopic and optical properties of synthetic (−)-**8** matched those reported for natural (−)-theobroxide.[24]

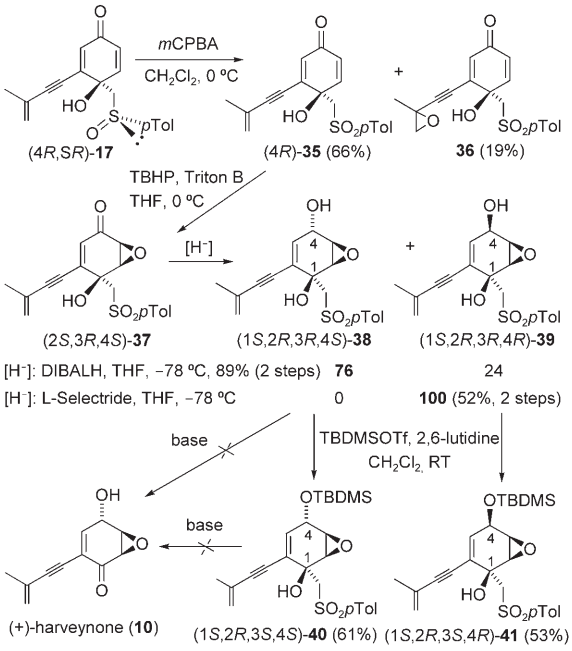
Regioselective *trans*-diaxial opening of the epoxide moiety in (+)-epiepoformin (**7**), with attack of an oxygenated nucleophile at C2, would give rise to the other target (+)-4-epigabosine A (**9**) (Scheme 7). Acidic hydrolytic opening (H_2SO_4, dioxane, H_2O) of epoxide **7** proved to be unsuccessful, while the use of the Ti(O*i*Pr)$_4$/propionic acid system[47] also did not provide the expected triol. It appears likely that the competitive complexation of the titanium with the epoxide oxygen and the ketone or carbinol oxygens before nucleophilic attack must be obstructing the reaction on a defined species. Finally, heating of (+)-epiepoformin (**7**) with an aqueous solution of NaOAc allowed the isolation of a 45% yield of (4*S*,5*R*,6*S*)-(**9**) {$[\alpha]_D^{20} = +169$ (c = 0.19 in MeOH)}, or 4-epigabosine A, after flash chromatography. The regioselective opening of the epoxide at C2 by NaOAc must be favoured by stereoelectronic factors when the reacting conformer of cyclohexenone **7**, shown in Scheme 7, is axially attacked by the nucleophile. The stereochemistry of compound **9** was established from the NMR parameters, mainly the value of the coupling constant between H-2 and H-3 (11.0 Hz), which is consistent with a *trans*-diaxial disposition of the two hydrogens in the more stable half-chair conformation, situating the three OH groups in an equatorial disposition.

Having completed these syntheses, we next focused on the natural cyclohexenone (+)-harveynone (**10**, Scheme 8).

When the starting *p*-quinol (4*R*,S*R*)-**17** was subjected to *m*CPBA oxidation, a mixture of sulfone **35** and sulfonyl epoxide **36** (mixture of diastereomers) was formed, and this was separated by flash chromatography to provide a 66% yield of (4*R*)-**35** and a 19% yield of **36**. The TBHP/Triton B treatment of pure **35** gave a clean reaction mixture in which the exclusive product was the epoxide (2*S*,3*R*,4*S*)-**37**, resulting from reaction at the unsubstituted C5=C6 double bond of **35**. The observed high π-facial diastereoselectivity was probably due to the presence of the allylic OH at C4, directing the epoxidation process from the same side. Although the crude yield was almost quantitative, chromatographic purification of **37** resulted in significant decomposition, so we continued the synthesis without further purification. Reduction of the carbonyl group in **37** with DIBALH gave a 76:24 mixture of diastereomeric alcohols (1*S*,2*R*,3*R*,4*S*)-**38** and (1*S*,2*R*,3*R*,4*R*)-**39** (89% overall yield for the last two steps). We also observed significant decomposition during chromatographic separation of these products, it being possible to isolate pure **38** and **39** in only 15 and 10% yields, respectively. When the reduction of **37** was performed with L-Selectride, epimer **39** was the only detected product and could be isolated in 52% yield. Again, however, chromatographic purification resulted in only a 19% yield of pure **39**. The stereochemical outcomes of these reductions on cyclohexenone **37** were very similar to that observed for derivative **31**.

Unfortunately, all trials directed towards recovery of the masked carbonyl groups at C1 in **38** and **39** with use of different bases [Cs_2CO_3, $Ba(OH)_2$, *t*BuOK, NaH and *n*BuLi] and temperatures were unsuccessful, and harveynone (**10**) was never detected. Although $MeSO_2pTol$ was always present in the final reaction mixtures, only products corresponding to decomposition of the cyclohexenone moiety were observed. Use of weaker bases such as $NaHCO_3$ or iPr_2NH left the starting material unchanged. We next proceeded to protect the OH moieties in **38** and **39** (TBDMSOTf, 2,6-lutidine) as the corresponding OTBDMS derivatives, to give (1S,2*R*,3*S*,4*S*)-**40** (61%) and (1S,2*R*,3*S*,4*R*)-**41** (53%), but, again, treatment with different bases only afforded $MeSO_2pTol$ and decomposition products. Looking at the literature, we found that precedent instability of several epoxyquinols[28] similar to harveynone in basic media had been observed. Our data clearly show that the presence of the alkynyl substituent in derivatives **38**–**41** could be responsible for this instability, by increasing the acidity of the C4 allylic hydrogen and resulting in the observed decomposition under the basic conditions.

This failure illustrated that our approach, based on stereoselective organoaluminium additions to sulfinyl *p*-quinols in combination with retroaddition of methyl *p*-tolylsulfone to recover carbonyl groups, cannot be applied when the final structure is sensitive to the basic medium necessary to effect this transformation.



Scheme 8. Synthetic approaches to natural cyclohexenone (+)-harveynone (**10**).

Conclusion

In summary, we report the total enantioselective syntheses of the natural polyoxygenated cyclohexanes (−)-dihydroepiepoformin (**5**) and (−)-gabosine O (**6**), starting from 4-hydroxy-4-[(*p*-tolylsulfinyl)methyl]cyclohexa-2,5-dienone (S*R*)-**13**, in seven steps and 24 and 28% overall yields, respectively. The enantiomer of (−)-dihydroepiepoformin, (+)-**5**, was in turn available from *p*-quinol (S*S*)-**13** in 32% overall yield. Two other natural targets, each containing a methyl substituent in its cyclohexene structure, (+)-epiepoformin (**7**) and (−)-theobroxide (**8**), were obtained from the 4-hydroxy-3-methyl-4-[(*p*-tolylsulfinyl)methyl]cyclohexa-2,5-dienone (4*R*,S*R*)-**15**, also by proceeding from *p*-quinol (S*R*)-**13**, in six and seven steps from **13** and in 12 and 11% overall yields, respectively. (+)-4-Epigabosine A (**9**), an epimer of the natural product gabosine A, was obtained by controlled opening of the epoxide fragment present in (+)-epiepoformin (**7**). The successful route presented employed the chemo- and stereoselective addition of Me_3Al to (S*R*)- or (S*S*)-[(*p*-tolylsulfinyl)methyl]-*p*-quinol (**13**) and the elimination of the chiral sulfoxide as methyl *p*-tolylsulfone in the advanced β-hydroxy sulfone intermediates as the key steps for the synthesis of enantiopure cyclohexanes or cyclohexenes. Although the controlled chemo- and diastereoselective addition of an enyne aluminium derivative to (S*R*)-**13** was also achieved, the presence of the alkynyl substituent on the cyclohexene moiety prevented the isolation of the final cyclohexenone in the last steps, it not being possible to apply our methodology to complete the enantioselective synthesis of natural (+)-harveynone (**10**).

Experimental Section

General: Melting points were obtained in open capillary tubes and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively; diastereoisomeric ratios were established by integration of well separated signals of both diastereomers in the crude reaction mixtures. All reactions were monitored by thin-layer chromatography performed on precoated silica gel 60 sheets, while flash column chromatography was carried out on silica gel 60 (Merck, 230–400 mesh); eluting solvents are indicated in the text. The apparatus for inert atmosphere experiments was flame-dried under a stream of dry argon. THF and CH_2Cl_2 were dried over 4 Å molecular sieves, diisopropylamine was distilled from KOH. All other reagent-quality solvents were used without purification. For routine workup, hydrolysis was carried out with water, extraction with CH_2Cl_2, and solvent drying with $MgSO_4$. Full details for the synthesis of (S*S*)-**13**, (4*R*,5*R*,S*S*)-**19**, (4*R*,5*R*)-**20**, (1*R*,4*S*,6*R*)-**21**, (1*R*,4*S*,6*R*)-**23**, (4*S*,6*R*)-**24** (see reference [,12b]) and **14** and (4*R*,S*R*)-**15** (see ref. [,11b]) have been reported previously.

(S*R*)-4-Hydroxy-4-[(*p*-tolylsulfinyl)methyl]cyclohexa-2,5-dienone (13): A solution of *n*-butyllithium (2.4 M in hexanes, 32 mL, 80.0 mmol) was added under argon at −78 °C to a solution of freshly distilled diisopropylamine (12.3 mL, 88.0 mmol) in THF (150 mL). After the system had been stirred for 30 min, a solution of (S*R*)-methyl-*p*-tolylsulfoxide[32] (11.3 g, 73.5 mmol) in THF (120 mL) was added at −78 °C. After 30 min, a solution of 4,4-dimethoxycyclohexa-2,5-dienone[33c] (11.9 g, 77.0 mmol) in THF (265 mL) was slowly added and the mixture was stirred for two hours at −78 °C. The mixture was hydrolysed with a saturated aqueous solution of ammonium chloride (40 mL) and the organic layer was extracted with EtOAc. After workup, the crude product was dissolved in THF (40 mL) and a solution of oxalic acid (1.0 g, 11.1 mmol) in water (20 mL) was added. After the system had been stirred for 2 h, hydrolysed with a saturated solution of $NaHCO_3$, extracted with EtOAc, and worked up, the residue was recrystallized from EtOAc/hexane, giving compound (S*R*)-**13** as a white solid (15.4 g, 76 %). M.p. 141–143 °C; $[\alpha]_D^{20} = +144$ ($c = 1$ in $CHCl_3$); ^{1}H NMR: $\delta = 7.54$ and 7.36 (AA′BB′ system, 4H), 7.25 (dd, $J = 10.2$, 3.2 Hz, 1H), 7.00 (dd, $J = 10.2$, 3.2 Hz, 1H), 6.29 (dd, $J = 10.2$, 1.8 Hz, 1H), 6.18 (dd, $J = 10.1$, 1.9 Hz, 1H), 4.93 (s, 1H), 3.16 and 2.85 (AB system, $J = 13.3$ Hz, 2H), 2.43 ppm (s, 3H); ^{13}C NMR: $\delta = 184.9$, 149.2, 149.1, 142.2, 139.6, 130.1 (2C), 128.1, 127.6, 123.9 (2C), 68.0, 67.1, 21.3 ppm; elemental analysis calcd (%) for $C_{14}H_{14}O_3S$: C 64.10, H 5.38; found: C 63.63, H 5.10.

(4*R*,S*R*)-4-Hydroxy-3-(3-methylbut-3-en-1-ynyl)-4-[(*p*-tolylsulfinyl)methyl]cyclohexa-2,5-dienone (17) and (4*S*,S*R*)-18: A solution of *n*-butyllithium (2.4 M in hexanes, 21.0 mL, 53.0 mmol) was added under argon at 0 °C to a solution of commercially available 3-methylbut-3-en-1-yne (5.8 mL, 53.0 mmol) in hexane (122 mL). After 30 min, a solution of $AlMe_2Cl$ (1 M in hexane, 53 mL, 53.0 mmol) was added and the mixture was stirred for 30 min at room temperature. The reaction mixture was diluted with CH_2Cl_2 (122 mL) and a solution of (S*R*)-**13** (2.8 g, 11.0 mmol) in CH_2Cl_2 (60 mL) was added. After the system had been stirred for 3 h, the mixture was cooled to −78 °C and a solution of freshly recrystallized *N*-bromosuccinimide (5.6 g, 32.0 mmol) in THF (50 mL) was added. After 1 h at −78 °C, the excess of aluminium reagent was destroyed with MeOH, and the mixture was poured into an Erlenmeyer containing EtOAc and a saturated solution of sodium potassium tartrate and stirred vigorously for 1 h. The aqueous layer was extracted twice with EtOAc and the combined organic layers were washed with a saturated solution of $Na_2S_2O_8$. After workup, an inseparable mixture of two bromo derivatives **16** (5.0 g, 12.5 mmol) was obtained. This mixture was dissolved in DMF (60 mL), and LiBr (3.3 g, 38.0 mmol) and Li_2CO_3 (2.9 g, 39.0 mmol) were added. After heating at 100 °C for 1 h, the reaction mixture was hydrolysed with H_2O and extracted with EtOAc. After workup, the residue was purified by column chromatography (EtOAc/hexane 1:1), giving (4*R*,S*R*)-**17** as a yellow solid (2.3 g, 64 %), together with the corresponding 4-epimer (4*S*,S*R*)-**18**, also as a yellow oil (370 mg, 10 %).

Compound (4*R*,S*R*)-17: M.p. 126–127 °C (EtOAc/hexane); $[\alpha]_D^{20} = +269$ ($c = 0.5$ in acetone); ^{1}H NMR: $\delta = 7.51$ and 7.31 (AA′BB′ system, 4H), 7.35 (d, $J = 1.8$ Hz, 1H), 6.41–6.36 (m, 1H), 6.34 (dd, $J = 12.9$, 1.8 Hz, 1H), 5.46 (dq, $J = 1.6$, 1.2 Hz, 1H), 5.42 (dq, $J = 1.6$, 1.2 Hz, 1H), 4.92 (s, 1H), 3.46 and 2.96 (AB system, $J = 13.3$ Hz, 2H), 2.42 (s, 3H), 1.94 ppm (dd, $J = 1.4$, 1.0 Hz, 3H); ^{13}C NMR: $\delta = 184.2$, 148.1, 142.7, 142.6, 139.9, 131.8, 130.3 (2C), 128.3, 125.7, 125.4, 123.9 (2C), 103.3, 83.9, 69.8, 66.4, 22.9, 21.4 ppm: MS (EI): *m*/*z*: calcd for $C_{19}H_{18}O_3S$: 326.0977; found: 326.0970 $[M]^+$; MS (EI): *m*/*z* (%): 326 (1) $[M]^+$, 187 (15), 170 (23), 142 (15), 139 (60), 137 (100), 115 (32), 91 (69), 65 (39).

Compound (4*S*,S*R*)-18: $[\alpha]_D^{20} = +160$ ($c = 0.5$ in acetone); ^{1}H NMR: $\delta = 7.55$ and 7.35 (AA′BB′ system, 4H), 7.13 (d, $J = 10.3$ Hz, 1H), 6.41 (d, $J = 1.8$ Hz, 1H), 6.19 (dd, $J = 10.1$, 1.8 Hz, 1H), 5.56 (dq, $J = 1.8$, 1.0 Hz, 1H), 5.47 (dq, $J = 1.6$, 1.2 Hz, 1H), 4.54 (br s, 1H), 3.06 (s, 2H), 2.42 (s, 3H), 2.00 ppm (dd, $J = 1.6$, 1.2 Hz, 3H); ^{13}C NMR: $\delta = 184.2$, 148.6, 143.4, 142.3, 140.4, 131.6, 130.3 (2C), 127.6, 125.8, 124.0 (2C), 123.9, 104.4, 84.1, 70.5, 66.1, 22.7, 21.4 ppm; MS (EI): *m*/*z*: calcd for $C_{19}H_{18}O_3S$: 326.0977; found: 326.0975; MS (EI): *m*/*z* (%): 326(1) $[M]^+$, 187 (14), 171 (30), 142 (11), 139 (56), 137 (100), 115 (29), 91 (66), 65 (37).

(4*S*,5*S*,S*R*)-4-Hydroxy-5-methyl-4-[(*p*-tolylsulfinyl)methyl]cyclohex-2-enone (19): A solution of (S*R*)-**13** (664 mg, 2.5 mmol) in CH_2Cl_2 (13 mL) was added under argon at −78 °C to a solution of Me_3Al (2 M in hexane, 5.0 mL, 10.0 mmol) in CH_2Cl_2 (13 mL). After 4 h at the same temperature, the excess of Me_3Al was destroyed with methanol, and the mixture was poured into an Erlenmeyer containing EtOAc and a saturated solution of sodium potassium tartrate and stirred vigorously for 30 min. The organic layer was washed with brine and dried over $MgSO_4$. After workup and flash chromatography (EtOAc/hexane 1:1), (4*S*,5*S*,S*R*)-**19** was obtained as a white solid (500 mg, 76 %). M.p. 119–121 °C (EtOAc/hexane); $[\alpha]_D^{20} = +236$ ($c = 1$ in $CHCl_3$); ^{1}H NMR: $\delta = 7.56$ and 7.38 (AA′BB′ system, 4H), 7.25 (d, $J = 10.2$ Hz, 1H), 6.10 (dd, $J = 10.2$ Hz, 1H), 4.85 (s, 1H), 3.22 and 2.92 (AB system, $J = 12.2$ Hz, 2H), 2.62–2.22 (m, 3H), 2.44 (s, 3H), 1.10 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C NMR: $\delta = 198.3$, 149.7, 142.4, 139.7, 130.3 (2C), 129.0, 123.8 (2C), 71.6, 64.9, 41.7, 38.8, 21.3, 14.2 ppm; elemental analysis calcd (%) for $C_{15}H_{18}O_3S$ (278.4): C 64.72, H 6.52, S 11.52; found: C 64.69, H 6.85, S 11.89.

General procedure for *m*CPBA oxidations—Method A: A solution of *m*CPBA (1.2 equiv) in CH_2Cl_2 (0.5 M) was added at 0 °C to a solution of the corresponding sulfoxide (1 equiv) in CH_2Cl_2 (0.5 M). After stirring at 0 °C for 1–2 h, the mixture was hydrolysed with a saturated aqueous solution of Na_2SO_3 and extracted with CH_2Cl_2, and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$. After workup, the residue was purified by crystallization (EtOAc/hexane).

General procedure for reductions with DIBALH—Method B: A solution of the appropriate carbonyl compound (1 equiv) in THF (0.3 M) was added dropwise under argon at −78 °C to a solution of DIBALH (1 M in hexane, 3 equiv) in THF (0.2 M). After 30 min at the same temperature, the excess of DIBALH was destroyed with methanol, and the mixture was poured into an Erlenmeyer containing EtOAc and a saturated solution of sodium potassium tartrate and stirred vigorously for 30 min. The organic layer was washed with brine and dried over $MgSO_4$. After workup, the residue was recrystallized or purified by flash chromatography.

General procedure for reductions with L-Selectride—Method C: A solution of the appropriate carbonyl compound (1 equiv) in THF (0.3 M) was added at −78 °C to a solution of L-Selectride (1 M in THF, 3 equiv). After stirring at the same temperature for 1–2 h, the mixture was sequentially treated with H_2O, MeOH, NaOH (5 %), and H_2O_2. After several extractions with EtOAc and workup, the residue was purified by flash chromatography.

General procedure for OH protection as OTBDMS—Method D: 2,6-Lutidine (2.5 equiv) and TBDMSOTf (1.5 equiv) were sequentially added under argon at 0 °C to a solution of the appropriate alcohol (1 equiv) in CH_2Cl_2 (0.5 M). After stirring for 4–5 h, the reaction mixture was treated with HCl (5 %). After workup, the residue was purified by flash chromatography.

General procedure for $MeSO_2$*p*Tol elimination—Method E: Cs_2CO_3 (2–3 equiv) was added to a solution of the appropriate β-hydroxy sulfone (1 equiv) in CH_3CN (0.1 M). After the time indicated in each case, the reaction mixture was filtered through Celite and the solvent was evaporated to afford a residue, which was purified by flash chromatography.

General procedure for cyclohexenone epoxidation—Method F: Ph_3COOH[42] (5 equiv) and a solution of Triton B in MeOH (40%, 3 drops) were sequentially added at −78°C to a solution of the appropriate cyclohexenone (1 equiv) in THF (0.2 M), and the reaction mixture was allowed to warm to the desired temperature (Table 1). Once the starting material had been consumed (TLC), the mixture was treated with a saturated aqueous solution of Na_2SO_3 and extracted with diethyl ether. After workup, the residue was purified by flash chromatography.

General procedure for OTBDMS removal—Method G: A solution of $Bu_4N^+F^-$ (1 M in THF, 1.1 equiv) was added at 0°C to a solution of the appropriate OTBDMS derivative (1 equiv) in THF (0.3 M). After the system had been stirred for 30 min, a saturated aqueous solution of NH_4Cl was added and the mixture was extracted with CH_2Cl_2. After workup, the residue was purified by flash chromatography.

(4*S*,5*S*)-4-Hydroxy-5-methyl-4-[(*p*-tolylsulfonyl)methyl]cyclohex-2-enone (20): Compound (4*S*,5*S*)-**20** was obtained from (4*S*,5*S*,S*R*)-**19** (2.0 g, 6.9 mmol) by Method A, as a white solid (2.1 g, 98%). M.p. 144–146°C (EtOAc/hexane); $[\alpha]_D^{20} = +21.2$ ($c = 1$ in acetone); ^{1}H NMR: $\delta = 7.80$ and 7.39 (AA′BB′ system, 4H), 7.06 (dd, $J = 0.9$, 10.2 Hz, 1H), 5.96 (d, $J = 10.2$ Hz, 1H), 4.08 (brs, 1H), 3.50 and 3.45 (AB system, $J = 14.2$ Hz, 2H), 2.62–2.37 (m, 3H), 2.47 (s, 3H), 1.09 ppm (d, $J = 6.6$ Hz, 3H); ^{13}C NMR: $\delta = 197.8$, 148.9, 145.6, 137.4, 130.2 (2C), 129.1, 127.6 (2C), 71.7, 62.7, 42.0, 38.3, 21.7, 14.5 ppm; MS (FAB): *m*/*z*: calcd for $C_{15}H_{19}O_4S$: 295.1004; found: 295.1007 $[M+H]^+$; MS (FAB): *m*/*z* (%): 295 (51) $[M+H]^+$, 277 (77), 257 (66), 239 (54), 215 (60), 203 (76), 189 (94), 171 (100).

(1*S*,4*R*,6*S*)-6-Methyl-1-[(*p*-tolylsulfonyl)methyl]cyclohex-2-ene-1,4-diol (21): Compound (1*S*,4*R*,6*S*)-**21** was obtained from (4*S*,5*S*)-**20** (312 mg, 1.1 mmol) by Method B, as a white solid (298 mg, 95%). M.p. 118–119°C (EtOAc/hexane); $[\alpha]_D^{20} = +56.0$ ($c = 1$ in acetone); ^{1}H NMR (CD_3OD): $\delta = 7.76$ and 7.40 (AA′BB′ system, 4H), 5.73 (dd, $J = 2.0$, 10.2 Hz, 1H), 5.63 (dt, $J = 10.2$, 1.6 Hz, 1H), 4.14 (m, 1H), 3.49 and 3.40 (AB system, $J = 14.5$ Hz, 2H), 2.43 (s, 3H), 2.13–2.00 (m, 1H), 1.70 (m, 1H), 1.48 (ddd, $J = 10.1$, 12.3, 12.6 Hz, 1H), 0.94 ppm (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (CD_3OD): $\delta = 146.2$, 139.4, 135.5, 132.2, 130.9 (2C), 129.1 (2C), 70.8, 68.1, 63.9, 36.8, 35.6, 21.5, 15.4 ppm; elemental analysis calcd (%) for $C_{15}H_{20}O_4S$ (296.1): C 60.79, H 6.80, S 10.82; found: C 60.67, H 6.48, S 10.68.

(1*S*,4*S*,6*S*)-6-Methyl-1-[(*p*-tolylsulfonyl)methyl]cyclohex-2-ene-1,4-diol (22): Compound (1*S*,4*S*,6*S*)-**22** was obtained from (4*S*,5*S*)-**20** (80 mg, 0.28 mmol) by Method C, after chromatographic separation (CH_2Cl_2/acetone 5:1) of the resulting 60:40 mixture of (1*S*,4*R*,6*S*)-**21** and (1*S*,4*S*,6*S*)-**22**, as a colourless oil (20 mg, 30%). $[\alpha]_D^{20} = -30.0$ ($c = 1$ in acetone); ^{1}H NMR: $\delta = 7.79$ and 7.77 (AA′BB′ system, 4H), 6.06 (d, $J = 10.2$ Hz, 1H), 5.89 (dd, $J = 10.1$, 4.7 Hz, 1H), 4.23–4.16 (m, 1H), 3.48 and 3.36 (AB system, $J = 14.1$ Hz, 2H), 3.41 (s, 1H), 2.44 (s, 3H), 2.38–2.20 (m, 1H), 1.91 (ddd, $J = 14.1$, 4.63, 3.7 Hz, 1H), 1.61 (dt, $J = 14.1$, 3.96 Hz, 1H), 1.00 ppm (d, $J = 6.3$ Hz, 3H); ^{13}C NMR: $\delta = 145.0$, 138.1, 132.2, 130.9, 130.0 (2C), 127.6 (2C), 71.1, 63.7, 63.5, 35.7, 33.8, 21.6, 14.3 ppm.

(1*S*,4*R*,6*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-1-[(*p*-tolylsulfonyl)-methyl]cyclohex-2-en-1-ol (23): Compound (1*S*,4*R*,6*S*)-**23** was obtained from (1*S*,4*R*,6*S*)-**21** (152 mg, 0.53 mmol) by Method D, after flash chromatography (EtOAc/hexane 1:3), as a white solid (196 mg, 93%). M.p. 145–147°C (Et_2O/hexane); $[\alpha]_D^{20} = +47.0$ ($c = 1$ in acetone); ^{1}H NMR: $\delta = 7.79$ and 7.35 (AA′BB′ system, 4H), 5.94 (d, $J = 10.2$ Hz, 1H), 5.70 (dd, $J = 3.2$, 10.2 Hz, 1H), 4.21 (m, 1H), 3.60 (s, 1H), 3.53 and 3.31 (AB system, $J = 14.5$ Hz, 2H), 2.44 (s, 3H), 2.32 (m, 1H), 1.89 (ddd, $J = 5.4$, 8.1, 13.5 Hz, 1H), 1.56 (ddd, $J = 3.2$, 5.3, 13.5 Hz, 1H), 1.00 (d, $J = 7.0$ Hz, 3H), 0.87 (s, 9H), 0.05 ppm (s, 6H); ^{13}C NMR: $\delta = 144.9$, 138.3, 131.9, 130.8, 129.9 (2C), 127.6 (2C), 71.6, 64.1, 63.8, 36.5, 34.5, 25.9, 25.8 (3C), 21.6, 18.2, 14.3, −4.5 (2C) ppm.

(4*R*,6*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-methylcyclohex-2-enone (24): Compound (4*R*,6*S*)-**24** was obtained from (1*S*,4*R*,6*S*)-**23** (80 mg, 0.19 mmol) by Method E (17 h), after flash chromatography (EtOAc/hexane 3:1), as a colourless oil (42 mg, 89%). $[\alpha]_D^{20} = +67.0$ ($c = 0.4$ in acetone); ^{1}H NMR: $\delta = 6.77$ (dt, $J = 10.1$, 2.0 Hz, 1H), 5.91 (dd, $J = 2.4$, 10.1 Hz, 1H), 4.59 (m, 1H), 2.38 (m, 1H), 2.21 (m, 1H), 1.77 (dt, $J = 10.5$, 12.5 Hz, 1H), 1.14 (d, $J = 6.5$ Hz, 3H), 0.91 (s, 9H), 0.12 ppm (s, 6H); ^{13}C NMR: $\delta = 201.1$, 154.1, 128.3, 68.1, 41.9, 40.2, 25.7 (3C), 18.1, 15.0, −3.5, −3.7 ppm; MS (EI): *m*/*z*: calcd for $C_9H_{15}O_2Si$: 183.0841; found: 183.0844 $[M-C_4H_9]^+$; MS (EI): *m*/*z* (%): 183 (99) $[M-C_4H_9]^+$, 165 (7), 139 (13), 113 (11), 85.9 (40), 84 (62), 75 (100).

(2*R*,3*S*,4*R*,6*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-6-methylcyclohexanone (25) and (2*S*,3*R*,4*R*,6*S*)-26: A 25:75 mixture of compounds (2*R*,3*S*,4*R*,6*S*)-**25** and (2*S*,3*R*,4*R*,6*S*)-**26** was obtained from (4*R*,6*S*)-**24** (129 mg, 0.53 mmol) by Method F (−78 to −30°C), after flash chromatography (EtOAc/hexane 1:10), as a colourless oil in quantitative yield.

Compound (2*R*,3*S*,4*R*,6*S*)-25: ^{1}H NMR: $\delta = 4.45$ (dd, $J = 5.9$, 2.8 Hz, 1H), 3.41 (ddd, $J = 3.8$, 3.2, 1.0 Hz, 1H), 3.23 (d, $J = 3.6$ Hz, 1H), 2.45 (ddq, $J = 11.7$, 7.1, 7.1 Hz, 1H), 1.77 (dd, $J = 11.7$, 2.4 Hz, 1H), 1.73 (ddd, $J = 6.3$, 3.4, 1.2 Hz, 1H), 1.09 (d, $J = 7.1$ Hz, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.09 ppm (s, 3H).

Compound (2*S*,3*R*,4*R*,6*S*)-26: ^{1}H NMR: $\delta = 4.34$ (ddt, $J = 7.7$, 5.7, 1.0 Hz, 1H), 3.45 (dt, $J = 3.8$, 1.4 Hz, 1H), 3.29 (dd, $J = 3.8$, 0.6 Hz, 1H), 2.66 (ddq, $J = 11.1$, 6.9, 5.5 Hz, 1H), 2.17 (dtd, $J = 13.5$, 5.5, 1.4 Hz, 1H), 1.56 (ddd, $J = 13.5$, 10.9, 7.9 Hz, 1H), 1.00 (d, $J = 6.9$ Hz, 3H), 0.88 (s, 9H), 0.11 (s, 3H), 0.08 ppm (s, 3H); ^{13}C NMR (25:75 mixture of **25** and **26**): $\delta = 208.2$, 206.2, 65.8, 65.4, 63.2, 56.6, 55.4, 54.2, 41.0, 36.2, 34.6, 32.4, 25.6 (6C), 15.4 (2C), 15.0 (2C), −4.7, −4.8, −4.9, −5.0 ppm; MS (EI): *m*/*z*: calcd for $C_9H_{15}O_3Si$: 199.0790; found: 199.0783 $[M-C_4H_9]^+$; MS (EI): *m*/*z* (%): 199 (36) $[M-C_4H_9]^+$, 157 (41), 129 (20), 75 (100).

(2*R*,3*R*,4*R*,6*S*)-2,3-Epoxy-4-hydroxy-6-methylcyclohexanone (27) and (2*S*,3*S*,4*R*,6*S*)-(5) [(−)-dihydroepiepoformin]: Compounds (2*R*,3*R*,4*R*,6*S*)-**27** and (2*S*,3*S*,4*R*,6*S*)-**5** were obtained from a 25:75 mixture of (2*R*,3*S*,4*R*,6*S*)-**25** and (2*S*,3*R*,4*R*,6*S*)-**26** (138 mg, 0.54 mmol) by Method G, after flash chromatography (EtOAc/hexane 2:1), as colourless oils in 16 and 41% yield, respectively.

(2*R*,3*R*,4*R*,6*S*)-27: $[\alpha]_D^{20} = -90$ ($c = 0.96$ in $CHCl_3$); ^{1}H NMR (500 MHz): $\delta = 4.58$ (m, 1H), 3.56 (dt, $J = 3.6$, 0.8 Hz, 1H), 3.30 (d, $J = 3.5$ Hz, 1H), 2.50 (ddq, $J = 10.1$, 8.5, 7.1 Hz, 1H), 1.87 (dd, $J = 3.0$, 0.8 Hz, 1H), 1.86 (dd, $J = 10.2$, 2.9 Hz, 1H), 1.84 (brs, 1H), 1.14 ppm (d, $J = 7.1$ Hz, 3H); ^{13}C NMR: $\delta = 205.7$, 64.9, 56.1, 54.2, 36.2, 32.2, 15.4 ppm; MS (EI): *m*/*z*: calcd for $C_7H_{10}O_3$: 142.0628; found: 142.0633 $[M]^+$; MS (EI): *m*/*z* (%): 142 (1) $[M]^+$, 125 (6), 88 (110), 86 (63), 85 (100).

(2*S*,3*S*,4*R*,6*S*)-5: $[\alpha]_D^{20} = -21$ ($c = 1.2$ in acetone), $[\alpha]_D^{20} = -27$ ($c = 1.2$ in $CHCl_3$); ^{1}H NMR (500 MHz): $\delta = 4.45$ (brdt, $J = 8.7$, 5.9 Hz, 1H), 3.57 (ddd, $J = 3.7$, 1.8, 0.9 Hz, 1H), 3.34 (dd, $J = 3.8$, 0.9 Hz, 1H), 2.75 (ddq, $J = 11.8$, 6.7, 5.1 Hz, 1H), 2.37 (dddd, $J = 13.2$, 6.0, 5.0, 1.8 Hz, 1H), 1.85 (d, $J = 5.2$ Hz, 1H), 1.63 (ddd, $J = 13.4$, 12.0, 8.5 Hz, 1H), 1.04 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR: $\delta = 208.1$, 65.1, 63.1, 55.3, 41.4, 34.4, 14.6 ppm; MS (EI): *m*/*z*: calcd for $C_7H_{10}O_3$: 142.0628; found: 142.0628 $[M]^+$; MS (EI): *m*/*z* (%): 142 (1) $[M]^+$, 88 (10), 86 (66), 84 (100).

(2*S*,3*R*,4*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-6-methylcyclohexanone (25) and (2*R*,3*S*,4*S*,6*R*)-26: A 25:75 mixture of compounds (2*S*,3*R*,4*S*,6*R*)-**25** and (2*R*,3*S*,4*S*,6*R*)-**26** was obtained from (4*S*,6*R*)-**24**[12b] by Method F (−78 to −30°C), after flash chromatography (EtOAc/hexane 1:10), as a colourless oil in quantitative yield. The spectroscopic data were identical to those of their enantiomers (2*R*,3*S*,4*R*,6*S*)-**25** and (2*S*,3*R*,4*R*,6*S*)-**26**.

(2*S*,3*S*,4*S*,6*R*)-2,3-Epoxy-4-hydroxy-6-methylcyclohexanone (27) and (2*R*,3*R*,4*S*,6*R*)-5 [(+)-dihydroepiepoformin]: Compounds (2*S*,3*S*,4*S*,6*R*)-**27** and (2*R*,3*R*,4*S*,6*R*)-**5** were obtained from a 25:75 mixture of (2*S*,3*R*,4*S*,6*R*)-**25** and (2*R*,3*S*,4*S*,6*R*)-**26** by Method G, after flash chromatography (EtOAc/hexane 2:1), as colourless oils in 16 and 61% yield, respectively. The spectroscopic data were identical to those of their enantiomers.

(2*S*,3*S*,4*S*,6*R*)-27: $[\alpha]_D^{20} = +90$ ($c = 0.96$ in $CHCl_3$).

(2*R*,3*R*,4*S*,6*R*)-5: $[\alpha]_D^{20} = +22$ ($c = 0.1$ in acetone), $[\alpha]_D^{20} = +34$ ($c = 0.1$ in $CHCl_3$).

(2*R*,3*R*,4*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-dihydroxy-6-methylcyclohexanone (28) and (2*R*,3*R*,4*R*,6*S*)-29: H_2SO_4 (1 M, 21 μL, 0.002 mmol) was added to a solution of $NaIO_4$ (67 mg, 0.3 mmol) in H_2O (400 μL).

After all solids had dissolved, the solution was cooled to 0 °C, an aqueous solution of $RuCl_3$ (0.1 M, 10 μL, 0.002 mmol) was added, and the mixture was stirred until the colour had turned bright yellow. EtOAc (1.2 mL) was added, stirring was continued for 5 min, CH_3CN (1.2 mL) was added, and stirring was continued for a further 5 min. Compound (4*R*,6*S*)-**24** (50 mg, 0.2 mmol) was added in one portion and the reaction mixture was stirred for 10 min and then poured onto a mixture of saturated $NaHCO_3$ (5 mL) and saturated $Na_2S_2O_3$ (5 mL) solutions. Phases were separated, the aqueous layer was extracted with EtOAc (3×5 mL), and after workup the residue was purified by flash chromatography (EtOAc/hexane 1:2) to give an inseparable 58:42 mixture of (2*R*,3*R*,4*S*,6*R*)-**28** and (2*R*,3*R*,4*R*,6*S*)-**29** as a colourless oil (20 mg, 35 %). ^{1}H NMR (mixture of **28** and **29**): δ = 4.74 (d, *J* = 2.3 Hz, 1H), 4.29–4.26 (m, 1H), 4.23–4.17 (m, 4H), 3.74 (brs, 1H), 2.73 (dq, *J* = 2.3, 7.2 Hz, 1H), 2.66 (brs, 1H), 2.49–2.40 (m, 1H), 2.29 (ddd, *J* = 14.5, 6.6, 3.2 Hz, 1H), 1.98–1.93 (m, 1H), 1.76 (ddd, *J* = 14.5, 4.5, 2.4 Hz, 1H), 1.37 (d, *J* = 7.5 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), −0.12 (s, 18H), −0.91 ppm (s, 12H); ^{13}C NMR (mixture of **28** and **29**): δ = 214.3, 209.9, 75.1, 72.0, 70.3, 69.1, 41.7, 38.5, 37.3, 34.9, 25.7, 19.7, 18.1, 17.9, 13.4, −4.7, −4.8, −4.9, −5.1 ppm.

(4*R*,6*S*)-4-Hydroxy-6-methylcyclohex-2-enone (30): Compound (4*R*,6*S*)-**30** was obtained from (4*R*,6*S*)-**24** (706 mg, 2.94 mmol) by Method G, after flash chromatography (EtOAc/hexane 1:1), as a colourless oil (296 mg, 80 %). $[\alpha]_D^{20}$ = +78 (*c* = 0.68 in acetone); ^{1}H NMR: δ = 6.89 (ddd, *J* = 10.2, 1.9, 1.9 Hz, 1H), 5.95 (dd, *J* = 10.2, 2.4 Hz, 1H), 4.67 (brs, 1H), 2.40–2.32 (m, 3H), 1.70 (ddd, *J* = 10.5, 13.1, 14.6 Hz, 1H), 1.15 ppm (d, *J* = 6.5 Hz, 3H); ^{13}C NMR: δ = 201.5, 153.4, 128.4, 67.2, 41.3, 40.0, 14.8 ppm; MS (EI): *m*/*z*: calcd for $C_7H_{10}O_2$: 126.0681; found: 126.0684 $[M]^+$; MS (EI): *m*/*z* (%): 126 (16) $[M]^+$, 108 (19), 84 (100), 82 (35), 68 (12).

(2*R*,3*R*,4*R*,6*S*)-2,3,4-Trihydroxy-6-methylcyclohexanone (6) [(−)-gabosine O]: A solution of OsO_4 in CH_2Cl_2 (420 μL, 0.16 mmol) was added at −78 °C to a solution of (4*R*,6*S*)-**30** (20.0 mg, 0.16 mmol) and TMEDA (26 μL, 0.18 mmol) in CH_2Cl_2 (16 mL). After 1 h, the solution was concentrated under reduced pressure and the residue was dissolved in MeOH (10 mL). HCl (35 %, 5 drops) was added and the solution was stirred for 3 h. After workup and flash chromatography (EtOAc/EtOH 5:1), compound (2*R*,3*R*,4*R*,6*S*)-**6** [(−)-gabosine O] was isolated pure as a colourless oil (17.7 mg, 60 %). $[\alpha]_D^{20}$ = −11 (*c* = 0.15 in MeOH); ^{1}H NMR (CD_3OD): δ = 4.27 (dd, *J* = 3.0, 1.3 Hz, 1H), 4.22 (dd, *J* = 5.0, 2.3 Hz, 1H), 4.19 (ddd, *J* = 11.2, 4.6, 2.3 Hz, 1H), 2.54 (tdq, *J* = 12.7, 1.5, 6.5 Hz, 1H), 2.03 (ddd, *J* = 12.5, 6.0, 4.8 Hz, 1H), 1.84 (ddd, *J* = 13.2, 12.2, 11.2 Hz, 1H), 1.05 ppm (d, *J* = 6.5 Hz, 3H); ^{13}C NMR: δ = 212.2, 78.1, 76.9, 69.4, 39.8, 37.9, 14.1 ppm; MS (EI): *m*/*z*: calcd for $C_7H_{12}O_4$: 160.0736; found: 160.0741 $[M]^+$; MS (EI): *m*/*z* (%) 160 (5) $[M]^+$, 142 (5), 124 (12), 96 (17), 73 (100), 57 (45).

(4*R*)-4-Hydroxy-3-methyl-4-[(*p*-tolylsulfonyl)methyl]cyclohexa-2,5-dienone: This compound was obtained from (4*R*,S*R*)-**15**[11b] (503 mg, 1.82 mmol) by Method A, as a white solid (528 mg, 99 %). M.p. 122–123 °C (EtOAc/hexane); $[\alpha]_D^{20}$ = −70 (*c* = 0.5 in $CHCl_3$), $[\alpha]_D^{20}$ = +16 (*c* = 0.5 in acetone); ^{1}H NMR: δ = 7.68 and 7.31 (AA′BB′ system, 4H), 7.11 (d, *J* = 10.1 Hz, 1H), 6.01 (dd, *J* = 10.1, 2.0 Hz, 1H), 5.92 (dq, *J* = 1.4, 1.4 Hz, 1H), 4.4 (brs, 1H), 3.59 and 3.35 (AB system, *J* = 14.3 Hz, 2H), 2.4 (s, 3H), 1.96 ppm (d, *J* = 1.6 Hz, 3H); ^{13}C NMR: δ = 185.3, 158.3, 148.6, 145.5, 136.4, 130.0 (2C), 127.8 (2C), 127.5, 127.3, 69.2, 63.01, 21.6, 18.1 ppm; MS (EI): *m*/*z*: calcd for $C_{15}H_{16}O_4S$ 292.0769; found: 292.0779 $[M]^+$; MS (EI): *m*/*z* (%): 292 (3) $[M]^+$, 170 (50), 155 (29), 137 (34), 123 (36), 105 (42), 91 (100), 65 (39).

(2*S*,3*R*,4*S*)-2,3-Epoxy-4-hydroxy-5-methyl-4-[(*p*-tolylsulfonyl)methyl]cyclohex-5-enone (31): Compound (2*S*,3*R*,4*S*)-**31** was obtained from (4*R*)-4-hydroxy-3-methyl-4-[(*p*-tolylsulfonyl)methyl]cyclohexa-2,5-dienone (50 mg, 0.17 mmol) by Method F (changing Ph_3COOH for TBHP, 0 °C), after flash chromatography (EtOAc/hexane 1:1), as a white solid (37.7 mg, 72 %). M.p. 186–187 °C; $[\alpha]_D^{20}$ = −209 (*c* = 0.5 in acetone); ^{1}H NMR: δ = 7.74 and 7.37 (AA′BB′ system, 4H), 5.72 (dq, *J* = 3.4, 1.4 Hz, 1H), 4.14 (d, *J* = 4.0 Hz, 1H), 3.55 (d, *J* = 4.0 Hz, 1H), 3.54 (brs, 1H), 3.52 (AB system, *J* = 14.6 Hz, 2H), 2.46 (s, 3H), 1.83 ppm (d, *J* = 1.4 Hz, 3H); ^{13}C NMR: δ = 192.1, 154.5, 145.7, 136.9, 130.1 (2C), 127.9 (2C), 124.5, 71.4, 61.5, 58.0, 55.0, 21.7, 18.2 ppm; elemental analysis calcd (%) for $C_{15}H_{16}O_5S$: C 58.43, H 25.94, S 10.40; found: C 58.25, H 5.23, S 10.18.

(1*S*,2*R*,3*R*,4*S*)-2,3-Epoxy-6-methyl-1-[(*p*-tolylsulfonyl)methyl]cyclohex-5-ene-1,4-diol (32): Compound (1*S*,2*R*,3*R*,4*S*)-**32** was obtained from (2*S*,3*R*,4*S*)-**31** (50.0 mg, 0.16 mmol) by Method B, after chromatographic separation (EtOAc/hexane 3:1) of a 77:23 mixture of **32** and **33**, as a white solid (33.4 mg, 67 %). M.p. 140–141 °C; $[\alpha]_D^{20}$ = −7 (*c* = 0.5 in acetone); ^{1}H NMR: δ = 7.76 and 7.36 (AA′BB′ system, 4H), 5.64 (dq, *J* = 3.0, 1.4 Hz, 1H), 4.34 (ddd, *J* = 11.5, 5.1, 1.0 Hz, 1H), 3.66 (dd, *J* = 3.8, 2.0 Hz, 1H), 3.70 and 3.50 (AB system, *J* = 14.6 Hz, 2H), 3.55 (dd, *J* = 4.0, 1.0 Hz, 1H), 3.39 (d, *J* = 11.5 Hz, 1H), 2.79 (s, 1H), 2.45 (s, 3H), 1.65 ppm (d, *J* = 1.2 Hz, 3H); ^{13}C NMR: δ = 145.4, 137.1, 133.1, 130.0 (2C), 127.7 (2C), 125.6, 70.1, 63.0, 62.0, 58.5, 57.1, 21.6, 17.1 ppm; MS (MALDI): *m*/*z*: calcd for $C_{15}H_{18}O_5S$: 333.0767; found: 333.0775 $[M+Na]^+$.

(1*S*,2*R*,3*R*,4*R*)-2,3-Epoxy-5-methyl-1-[(*p*-tolylsulfonyl)methyl]cyclohex-5-ene-1,4-diol (33): Compound (1*S*,2*R*,3*R*,4*R*)-**33** was obtained from (2*S*,3*R*,4*S*)-**31** (50.0 mg, 0.16 mmol) by Method C, after flash chromatography (EtOAc/hexane 3:1), as a white solid (41.6 mg, 83 %). M.p. 145–146 °C; $[\alpha]_D^{20}$ = −60 (*c* = 0.5 in acetone); ^{1}H NMR: δ = 7.72 and 7.33 (AA′BB′ system, 4H), 5.29 (dd, *J* = 4.2 and 2.2 Hz, 1H), 4.50 (brs, 1H), 3.75 (d, *J* = 4.2 Hz, 1H), 3.71 (dd, *J* = 4.9, 2.4 Hz, 1H), 3.60 (brs, 1H), 3.50 and 3.44 (AB system, *J* = 14.6 Hz, 2H), 2.99 (d, *J* = 8.9 Hz, 1H), 2.43 (s, 3H), 1.55 ppm (d, *J* = 1.6 Hz, 3H); ^{13}C NMR: δ = 145.1, 137.3, 132.8, 129.8 (2C), 127.7 (2C), 125.9, 70.2, 65.2, 61.1, 59.2, 57.2, 21.6, 16.9 ppm; MS (MALDI): *m*/*z*: calcd for $C_{15}H_{18}O_5S$: 333.0767; found: 333.0771 $[M+Na]^+$.

(1*S*,2*R*,3*S*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-6-methyl-1-[(*p*-tolylsulfonyl)methyl]cyclohex-5-en-1-ol: This compound was obtained from (1*S*,2*R*,3*R*,4*S*)-**32** (35.0 mg, 0.11 mmol) by Method D, after flash chromatography (EtOAc/hexane 1:3), as a white solid (25 mg, 52 %). M.p. 110–111 °C; $[\alpha]_D^{20}$ = +8 (*c* = 0.5 in acetone); ^{1}H NMR: δ = 7.82 and 7.35 (AA′BB′ system, 4H), 5.34 (dq, *J* = 7.3, 1.6 Hz, 1H), 4.41 (ddd, *J* = 0.8, 2.2, 5.7 Hz, 1H), 3.96 (d, *J* = 1.6 Hz, 1H), 3.76 (brs, 1H), 3.55 and 3.45 (AB system, *J* = 14.6 Hz, 2H), 3.29 (dd, *J* = 4.2, 2.2 Hz, 1H), 2.45 (s, 3H), 1.69 (dd, *J* = 0.6, 2.2 Hz, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.06 ppm (s, 3H); ^{13}C NMR: δ = 145.1, 137.8, 136.4, 129.9 (2C), 127.9 (2C), 123.0, 72.5, 64.0, 62.5, 55.8, 54.5, 25.7 (3C), 21.6, 18.0, 17.3, −4.5, −4.9 ppm; MS (EI) *m*/*z*: calcd for $C_{20}H_{29}O_5SiS$: 409.1505; found: 409.1501 $[M-CH_3]^+$; MS (EI) *m*/*z* (%): 409 (2) $[M-CH_3]^+$, 367 (100), 149 (40), 91 (30), 75 (50).

(2*R*,3*S*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-6-methylcyclohex-5-enone (34): Compound (2*R*,3*S*,4*S*)-**34** was obtained from (1*S*,2*R*,3*S*,4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-2,3-epoxy-6-methyl-1-[(*p*-tolylsulfonyl)methyl]cyclohex-5-en-1-ol (25.0 mg, 0.06 mmol) by Method E (24 h), after flash chromatography (EtOAc/hexane 1:4), as a colourless oil (15 mg, 99 %). $[\alpha]_D^{20}$ = +148 (*c* = 1.5 in acetone); ^{1}H NMR: δ = 6.28 (m, 1H), 4.63 (dd, *J* = 2.2, 1.0 Hz, 1H), 3.63 (dd, *J* = 3.6, 1.2 Hz, 1H), 3.48 (d, *J* = 3.6 Hz, 1H), 1.83 (d, *J* = 1.4 Hz, 3H), 0.92 (s, 9H), 0.17 (s, 3H), 0.14 ppm (s, 3H); ^{13}C NMR: δ = 194.0, 139.5, 133.3, 64.0, 58.4, 53.4, 26.2, 25.7 (3C), 15.9, −4.4, −4.6; MS (EI): *m*/*z* (%): 254 (3) $[M]^+$, 253 (11), 197 (3), 169 (5), 115 (10), 73 (100).

(2*R*,3*R*,4*S*)-2,3-Epoxy-4-hydroxy-6-methylcyclohex-5-enone (7) [(+)-epiepoformin]: Compound (2*R*,3*R*,4*S*)-**7** was obtained from (1*S*,2*R*,3*R*,4*S*)-**32** (173 mg, 0.56 mmol) by Method E (30 min), after flash chromatography (EtOAc/hexane 1:1), as a white solid (42 mg, 54 %). M.p. 82–84 °C; $[\alpha]_D^{20}$ = +303 (*c* = 1.1 in EtOH), 96 % *ee*; ^{1}H NMR (500 MHz): δ = 6.47–6.44 (m, 1H), 4.66 (d, *J* = 4.4 Hz, 1H), 3.78 (ddd, *J* = 3.8, 2.5, 1.4 Hz, 1H), 3.51 (dd, *J* = 3.6, 1.3 Hz, 1H), 2.00 (brs, 1H), 1.85 ppm (d, *J* = 1.6 Hz, 3H); ^{13}C NMR (100 MHz): δ = 194.1, 138.7, 134.7, 63.5, 57.6, 53.4, 15.9 ppm.

(+)-Epiepoformin (**7**) was also obtained from compound (2*R*,3S,4*S*)-**34** (15.2 mg, 0.006 mmol) by Method G, after flash chromatography (EtOAc/hexane 2:1), as a colourless oil (3.4 mg, 41 %).

Synthesis of MTPA esters: Et_3N (10 μL, 0.07 mmol) was added to a solution of alcohol (2*R*,3*R*,4*S*)-**7** (5.0 mg, 0.04 mmol), DMAP (1 mg) and (*R*)- or (*S*)-MTPA-Cl (14.4 mg, 0.04 mmol) in dry CH_2Cl_2 (2.2 mL). The mixture was stirred for 1 h at room temperature and quenched with a satu-

rated solution of NH_4Cl, and the organic layer was washed successively with an aqueous solution of HCl (5%) and saturated $NaHCO_3$. After workup, the resulting mixture of diastereoisomeric esters was used directly for ^1H NMR analysis in $CDCl_3$.

(1*S*,2*R*,3*S*,4*R*)-2,3-Epoxy-5-methylcyclohex-5-ene-1,4-diol (8) [(−)-theobroxide]: $CeCl_3{\cdot}7H_2O$ (53 mg, 0.14 mmol) was added to a solution of (2*R*,3*R*,4*S*)-**7** (10 mg, 0.07 mmol) in MeOH (0.8 mL) and the resulting suspension was vigorously stirred for 1 h and then cooled to −78 °C. A solution of $NaBH_4$ (6 mg, 0.16 mmol) in MeOH (0.4 mL) was added and the reaction mixture was stirred at −78 °C for 30 min. After quenching with saturated aqueous $NaHCO_3$ solution, workup and flash chromatography (EtOAc), compound (1*S*,2*R*,3*S*,4*R*)-**8** was obtained as a white solid in quantitative yield. M.p. 62–64 °C; $[\alpha]_D^{20} = -8.0$ (c = 0.10 in EtOH); ^1H NMR: δ = 5.52–5.49 (m, 1H), 4.45–4.43 (m, 1H), 4.24 (brs, 1H), 3.36–3.34 (m, 1H), 3.30–3.37 (m, 1H), 1.82 ppm (s, 3H); ^{13}C NMR: δ = 135.2, 121.5, 66.2, 63.0, 53.0, 51.8, 21.2 ppm.

(4*S*,5*R*,6*S*)-4,5,6-Trihydroxy-2-methylcyclohex-2-enone (9) [(+)-4-epigabosine A]: A solution of (2*R*,3*R*,4*S*)-**7** (10 mg, 0.07 mmol) in water, containing sodium acetate (1.6 mg, 0.02 mmol), was heated at reflux for 2 d. After evaporation of the solvent and flash chromatography (EtOAc/EtOH 5:1), compound (4*S*,5*R*,6*S*)-**9** was obtained as a colourless oil (5.1 mg, 45%). $[\alpha]_D^{20} = +169$ (c = 0.19 in MeOH); ^1H NMR (CD_3OD): δ = 6.64 (dq, J = 3.2, 1.6 Hz, 1H), 4.28 (dd, J = 8.1, 2.1 Hz, 1H), 3.96 (d, J = 11.0 Hz, 1H), 3.51 (dd, J = 10.8, 8.1 Hz, 1H), 1.80 ppm (d, J = 1.6 Hz, 1H); ^{13}C NMR: δ = 200.1, 147.9, 134.7, 80.0, 78.0, 72.5, 15.2 ppm; MS (EI): m/z: calcd for $C_7H_{10}O_4$: 158.0579 $[M]^+$; found: 158.0585; MS (EI): m/z (%): 158 (1) $[M]^+$, 140 (18), 98 (100), 70 (64).

(4*R*)-4-Hydroxy-3-(3-methylbut-3-en-1-ynyl)-4-[(*p*-tolylsulfonyl)methyl]-cyclohexa-2,5-dienone (35): Compound (4*R*)-**35** was obtained from (4*R*,S*R*)-**17** (913 mg, 2.8 mmol) by Method A, after separation from epoxide **36** by flash chromatography (EtOAc/hexane 1:1), as a yellow solid, in 66% yield. M.p. 67–68 °C; $[\alpha]_D^{20} = +37$ (c = 0.51 in acetone); ^1H NMR: δ = 7.72 and 7.33 (AA′BB′ system, 4H), 7.18 (d, J = 9.9 Hz, 1H), 6.19 (t, J = 1.8 Hz, 1H), 6.16 (dd, J = 13.7, 2.0 Hz, 1H), 5.43–5.42 (m, 2H), 4.41 (brs, 1H), 3.80 and 3.63 (AB system, J = 14.3 Hz, 2H), 2.44 (s, 3H), 1.92 ppm (t, J = 1.2 Hz, 3H); ^{13}C NMR: δ = 184.4, 147.4, 145.3, 142.0, 136.3, 131.6, 129.7 (2C), 127.9 (2C), 127.6 (2C), 125.4, 103.2, 83.4, 67.9, 63.5, 22.6, 21.5 ppm; MS (EI): m/z (%): calcd for $C_{19}H_{18}O_4S$: 342.0926; found: 342.0922 $[M]^+$; MS (EI): m/z (%): 342 (5) $[M]^+$, 220 (12), 187 (36), 173 (37), 155 (25), 139 (16), 115 (25), 91 (100), 65 (41).

3-(3,4-Epoxy-3-methylbut-1-ynyl)-4-hydroxy-4-[(*p*-tolylsulfonyl)methyl]-cyclohexa-2,5-dienone (36): Compound **36** was obtained, as a mixture of diastereoisomers, from (4*R*,S*R*)-**18** (913 mg, 2.8 mmol) by Method A, after separation from sulfone **35** by flash chromatography (EtOAc/hexane 1:1), as a colourless oil (199 mg, 20%). $[\alpha]_D^{20} = +19$ (c = 0.52 in acetone); ^1H NMR: δ = 7.80 and 7.41 (AA′BB′ system, 4H), 7.28 (d, J = 10.3 Hz, 1H), 6.35 (dd, J = 4.5, 2.0 Hz, 1H), 6.25 (ddd, J = 10.3, 1.8, 0.6 Hz, 1H), 4.11 (brs, 1H), 3.80 and 3.49 (AB system, J = 14.1 Hz, 2H), 3.11 (d, J = 5.5 Hz, 1H), 2.90 (d, J = 5.5 Hz, 1H), 2.51 (s, 3H), 1.64 ppm (s, 3H); ^{13}C NMR: δ = 183.8, 147.0, 145.7, 140.6, 136.6, 135.4, 133.2, 130.2 (2C), 128.0 (2C), 127.8, 101.2, 68.5, 63.7, 63.6, 55.7, 22.3, 21.7 ppm; MS (EI): m/z: calcd for $C_{19}H_{18}O_5S$: 358.0875; found: 358.0872 $[M]^+$; MS (EI): m/z (%): 358 (2) $[M]^+$, 327 (11), 203 (15), 189 (29), 173 (58), 155 (46), 139 (26), 91 (100).

(2*S*,3*R*,4*S*)-2,3-Epoxy-5-(3-methylbut-3-en-1-ynyl)-4-[(*p*-tolylsulfonyl)methyl]cyclohex-5-enone (37): Compound (2*S*,3*R*,4S)-**37** was obtained from (4*R*)-**35** (10 mg, 0.03 mmol) by Method F [TBHP (7 μL, 0.03 mmol), 0 °C], as a yellow oil (8.8 mg, 84%). It was used without further purification in the next step. $[\alpha]_D^{20} = -143$ (c = 0.26 in acetone); ^1H NMR (500 MHz): δ = 7.74 and 7.35 (AA′BB′ system, 4H), 5.98 (d, J = 2.0 Hz, 1H), 5.41 (dq, J = 1.7, 1.6 Hz, 1H), 5.38 (dq, J = 1.6, 1.1 Hz, 1H), 4.18 (d, J = 3.9 Hz, 1H), 3.70 (AB system, J = 14.8 Hz, 2H), 3.63 (ddd, J = 4.1, 2.0, 0.5 Hz, 1H), 2.45 (s, 3H), 2.17 (s, 1H), 1.87 ppm (dd, J = 1.6, 1.1 Hz, 3H); ^{13}C NMR: δ = 191.4, 145.5, 138.6, 136.8, 130.0 (2C), 129.5, 128.1 (2C), 125.8, 125.5, 102.8, 83.3, 70.2, 62.1, 57.8, 54.9, 22.7, 21.7 ppm; MS (EI): m/z: calcd for $C_{15}H_{16}O_5S$: 358.0875; found: 358.0866 $[M]^+$; MS (EI): m/z (%): 358 (17) $[M]^+$, 203 (9), 161 (46), 139 (19), 91 (100), 65 (43).

(1*S*,2*R*,3*R*,4*S*)-2,3-Epoxy-6-(3-methylbut-3-en-1-ynyl)-1-[(*p*-tolylsulfonyl)methyl]cyclohex-5-ene-1,4-diol (38): Compound (1*S*,2*R*,3*R*,4*S*)-**38** was obtained from (2*S*,3*R*,4S)-**37** (99.3 mg, 0.29 mmol) by Method B, as a 76:24 mixture of epimers **38** and **39**, in 89% overall yield from (4*R*)-**35** (two steps). An analytical sample of pure **38** was obtained after flash chromatography (EtOAc/hexane 1:1) as a yellow solid. M.p. 102–103 °C; $[\alpha]_D^{20} = -43$ (c = 1.07 in acetone); ^1H NMR: δ = 7.72 and 7.35 (AA′BB′ system, 4H), 6.11 (dd, J = 5.1, 2.0 Hz, 1H), 5.25–5.23 (m, 1H), 5.22–5.21 (m, 1H), 4.46 (dd, J = 11.3, 5.3 Hz, 1H), 3.89 and 3.63 (AB system, J = 14.6 Hz, 2H), 3.70 (dd, J = 3.8, 0.8 Hz, 1H), 3.68 (dd, J = 1.8, 1.6 Hz, 1H), 2.43 (s, 3H), 1.81 ppm (dd, J = 1.2 and 1.0 Hz, 3H); ^{13}C NMR: δ = 145.1, 136.9, 133.8, 129.8 (2C), 127.6 (2C), 125.9, 122.8, 122.3, 92.9, 84.1, 68.7, 62.6, 62.5, 57.0, 56.1, 22.9, 21.4 ppm; MS (EI): m/z: calcd for $C_{19}H_{20}O_5S$: 360.1026; found: 360.1018 $[M]^+$; MS (EI): m/z (%): 360 (2) $[M]^+$, 187 (100), 159 (32), 115 (15), 91 (77).

(1*S*,2*R*,3*R*,4*R*)-2,3-Epoxy-6-(3-methylbut-3-en-1-ynyl)-1-[(*p*-tolylsulfonyl)methyl]cyclohex-5-ene-1,4-diol (39): Compound (1*S*,2*R*,3*R*,4*R*)-**39** was obtained from (2*S*,3*R*,4S)-**37** (8.8 mg, 0.026 mmol) by Method C, in 52% overall yield from (4*R*)-**35** (two steps), and was used without further purification in the next step. An analytical sample of pure **39** was obtained after flash chromatography (EtOAc/hexane 2:1), as a yellow solid. M.p. 42–43 °C; $[\alpha]_D^{20} = -29$ (c = 0.58 in acetone); ^1H NMR (500 MHz): δ = 7.71 and 7.29 (AA′BB′ system, 4H), 5.83 (dd, J = 2.4, 2.0 Hz, 1H), 5.23 (dq, J = 1.6, 1.2 Hz, 1H), 5.20 (dq, J = 2.0, 1.0 Hz, 1H), 4.60 (dd, J = 2.8 Hz, 1H), 3.84 (d, J = 4.2 Hz, 1H), 3.76 (ddd, J = 5.1, 2.8, 2.4 Hz, 1H), 3.70 and 3.55 (AB system, J = 14.6 Hz, 2H), 2.42 (s, 3H), 1.79 ppm (dd, J = 1.4, 1.2 Hz, 3H); ^{13}C NMR (500 MHz): δ = 144.9, 137.2, 135.3, 129.7 (2C), 127.9 (2C), 126.0, 123.0, 122.2, 92.5, 83.9, 68.9, 65.2, 61.7, 58.5, 56.9, 23.1, 21.6 ppm; MS (ES): m/z: calcd for $C_{19}H_{21}O_5S$: 361.1104; found: 361.1110 $[M+H]^+$; MS (ES): m/z (%): 361 (48) $[M+H]^+$, 187 (100), 159 (56), 139 (46).

(1*S*,2*R*,3*S*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-6-(3-methylbut-3-en-1-ynyl)-4-[(*p*-tolylsulfonyl)methyl]cyclohex-5-en-1-ol (40): Compound (1*S*,2*R*,3*S*,4*S*)-**40** was obtained from (1*S*,2*R*,3*R*,4*S*)-**38** (30 mg, 0.09 mmol) by Method D, after flash chromatography (EtOAc/hexane 1:3), as a yellow solid (25 mg, 61%). M.p. 93–94 °C; $[\alpha]_D^{20} = -8$ (c = 0.55 in acetone); ^1H NMR: δ = 7.85 and 7.32 (AA′BB′ system, 4H), 5.83 (dd, J = 5.4, 2.0 Hz, 1H), 5.26–5.24 (m, 2H), 4.50 (ddd, J = 5.4, 2.0, 0.8 Hz, 1H), 4.07 (dd, J = 4.0, 0.8 Hz, 1H), 3.72 and 3.55 (AB system, J = 14.8 Hz, 2H), 3.38 (ddd, J = 4.1, 2.2, 2.0 Hz, 1H), 3.25 (brs, 1H), 2.44 (s, 3H), 1.83 (dd, J = 1.5, 1.0 Hz, 3H), 0.90 (s, 9H), 0.14 (s, 3H), 0.11 ppm (s, 3H); ^{13}C NMR: δ = 144.8, 137.8, 132.4, 129.6 (2C), 128.3 (2C), 126.0, 124.1, 123.1, 93.8, 83.8, 70.3, 63.4, 62.8, 55.3, 55.0, 25.7 (3C), 23.0, 21.6, 18.1, −4.6, −4.9 ppm; MS (EI): m/z: calcd for $C_{25}H_{34}O_5SiS$: 474.1896; found: 474.1876 $[M]^+$; MS (EI): 474 (1) $[M]^+$, 459 (2), 417 (100), 301 (19), 285 (11), 213 (8), 187 (12), 149 (54), 91 (51), 73 (73).

(1*S*,2*R*,3*S*,4*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-6-(3-methylbut-3-en-1-ynyl)-1-[(*p*-tolylsulfonyl)methyl]cyclohex-5-en-1-ol (41): Compound (1*S*,2*R*,3*S*,4*R*)-**41** was obtained from (1*S*,2*R*,3*R*,4*R*)-**39** (60 mg, 0.17 mmol) by Method D, after flash chromatography (EtOAc/hexane 1:3), as a yellow solid (42 mg, 53%). M.p. 42–43 °C; $[\alpha]_D^{20} = -32$ (c = 0.42 in acetone); ^1H NMR: δ = 7.75 and 7.33 (AA′BB′ system, 4H), 5.73 (dd, J = 2.4, 2.2 Hz, 1H), 5.23–5.20 (m, 2H), 4.74 (dd, J = 2.4, 2.0 Hz, 1H), 3.79 (d, J = 4.2 Hz, 1H), 3.68 and 3.56 (AB system, J = 14.6 Hz, 2H), 3.61 (ddd, J = 4.2, 2.4, 2.0 Hz, 1H), 2.44 (s, 3H), 1.81 (dd, J = 1.6, 1.0 Hz, 3H), 0.93 (s, 9H), 0.17 ppm (s, 6H); ^{13}C NMR: δ = 144.9, 137.3, 135.9, 129.7 (2C), 127.8 (2C), 126.1, 122.7, 121.7, 92.2, 83.8, 69.3, 66.4, 61.6, 57.0, 56.5, 25.7 (3C), 23.1, 21.6, 18.2, −4.6, −4.7 ppm; MS (EI): m/z (%): calcd for $C_{25}H_{34}O_5SiS$: 474.1896; found: 474.1881 $[M]^+$; MS (EI): m/z (%): 474 (1) $[M]^+$, 465 (2), 447 (11), 417 (17), 365 (11), 324 (10), 301 (65), 261 (44), 243 (38), 193 (18), 149 (32), 91 (59), 73 (100).

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