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Cationic cyclization of keto-epoxides mediated by zirconium(IV) tetrachloride: diastereoselective synthesis of *cis*-decalinols

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ABSTRACT

10-Methyl-*cis*-9-decalinols are important motifs in several natural products and key intermediates in total synthesis. Herein, we wish to describe a highly chemo- and diastereoselective cyclization of keto-epoxides leading to 10-methyl-*cis*-9-decalinols. This method based on the use of zirconium(IV) tetrachloride permits the access to a wide variety of *cis*-decalinols in good to excellent yields. The cationic cyclization could also be performed with chiral keto-epoxide with complete control of the diastereoselectivity affording *cis*-bicyclic tertiary alcohol with good enantiomeric excess. The chemo- and the diastereoselectivity are assumed to result from the ability of Zr(IV) to generate highly stable bidentic complexes with α-hydroxy-ketone intermediates.

1. Introduction

In the course of our research program devoted to the total synthesis of (±)-triptolide **1**,[1,2] a natural product exhibiting an impressive array of biological activities, we were interested in the preparation of 10-methyl-*cis*-9-decalinol **2** (*cis*-configuration with respect of the vicinal arrangement of the hydroxyl-group and the methyl group) as key common intermediate to access **1**, and for the synthesis of *cis*-analogues library (Fig. 1). It is well known that dehydration of *cis*-[3] and *trans*-9-decalinol[4] derivatives followed by hydrogenolysis lead to *trans*-decalin skeletons highly stereoselectively, validating our convergent and modular approach for the synthesis of **1**. 10-Methyl-*cis*-9-decalinols are also prominent structural motifs found in numerous terpenoid natural products,[5,6] such as polypodine B **3**,[7] **4**[8] and **5**.[9] Additionally, substituted *cis*-bicyclic ketols surrogates are often used as versatile intermediates in a great number of total synthesis of natural compounds,[3,10] highlighting the crucial importance of these molecules in organic chemistry, and therefore the need for the development of selective strategies for their efficient preparation.

To address these issues, methodologies giving access to 10-methyl-*cis*-9-decalinols stereoselectively have been reported in literature.[12–19] The most common approach, pioneered by Fanta et al., is a modified Robinson annelation[3,10,11] based on the in situ condensation of cyclic ketones onto methylvinylketone followed by direct intramolecular aldolization reaction, affording bicyclic ketols in one-pot. The direct intramolecular aldolization of dicarbonyl systems has also been used recently by Nakada to construct highly functionalized bicyclic tertiary alcohols towards (−)-scabrone.[12] Besides these approaches, the copper-catalyzed domino reductive- or conjugated addition/indirect intramolecular aldol cyclizations developed by Riant,[13] Node[14] and Renaud[15] gave successfully access to a wide range of 10-methyl-*cis*-9-decalinols in an efficient manner. Quite recently Sakai et al. reported the use of an umpolung NHC-catalyzed intramolecular crossed benzoin reaction of cyclic 1,3-diketone aldehydes yielding, however in some instance, only moderate yields of 10-methyl-*cis*-9-decalinols.[16] Cascade cyclizations of naphthyl-substituted 1,3-diketones mediated by excess samarium diiodide–hexamethylphosphoramide complex was also described for the preparation of steroid-like compounds.[17] Additionally, the regioselective C–H bond oxidation of 10-methyl-*cis*-9-decalin could also be used for synthesizing 10-methyl-*cis*-9-decalinol, however only in low to moderate yields upon treatment with dimethyldioxirane or ruthenium porphyrin-2,6-dichloropyridine *N*-oxide system as oxidative agent.[18] Finally, the last important methodology developed three decades ago by Sutherland et al. is based on the intramolecular oxygen-directed carbocyclization of keto-epoxides under Lewis acid conditions.[19] However, cyclization results described so far are plagued with limitations, such as moderate yields and low chemoselectivity, due to the formation of ring contraction by-products leading to complex reaction mixtures.[19g] Although important progress in this area

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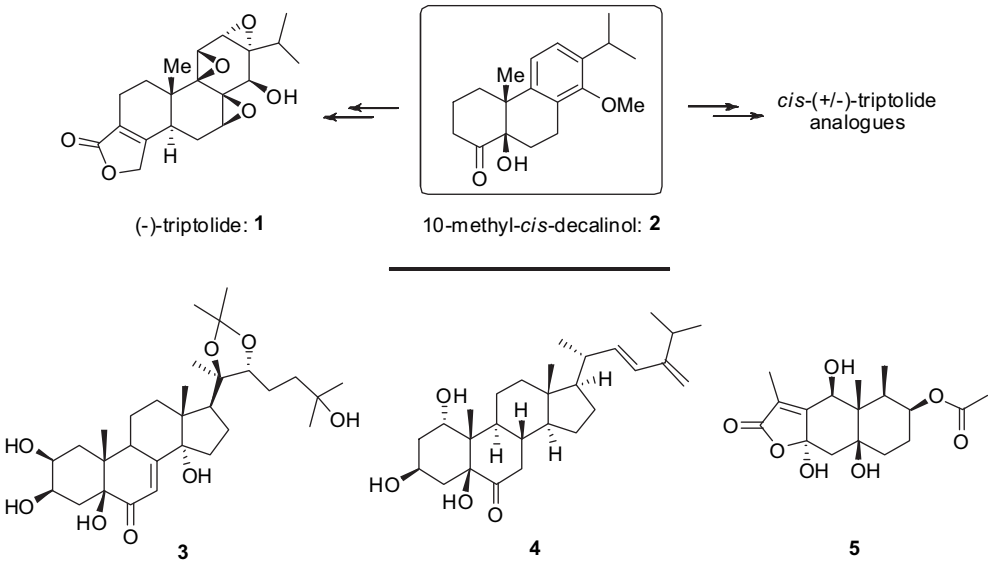


Fig. 1. Structures of 10-methyl-*cis*-9-decalinol **2** and natural products **1**, **3**, **4** and **5**.

has been realized, selective reactions are still restricted to limited substrates, and a general procedure of cyclization for keto-epoxides **6** has not been reported to date (Fig. 2). Hence, new chemo- and stereoselective methodologies to overcome these limitations for widespread synthetic applications of 10-methyl-*cis*-9-decalinols **7** are highly desirable.

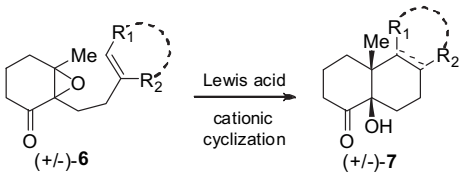


Fig. 2. Lewis acid promoted cyclization of keto-epoxide investigated.

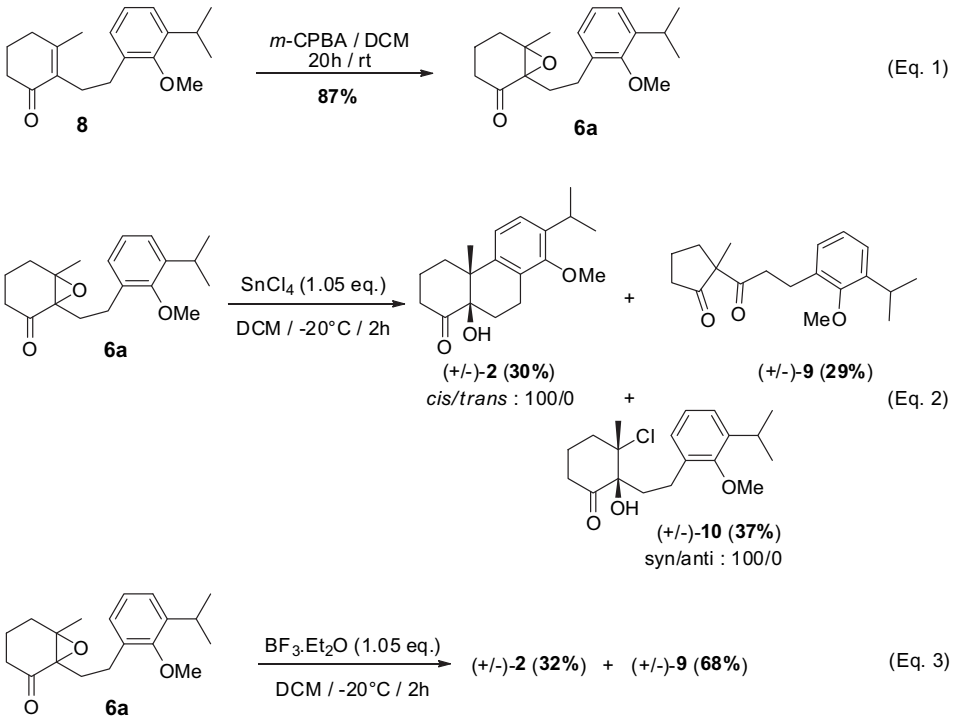
In continuation of our ongoing investigations on the total synthesis of (±)-triptolide and analogues,[20,21] we decided to reinvestigate this reaction in order to widen its application scope, and to explore possibly the asymmetric cationic cyclization version which has no literature report. Herein, we wish to report in full details our findings on the development of a general protocol for the efficient cyclization of functionalized keto-epoxides under the influence of $ZrCl_4$ as promoter, affording in good to excellent yields 10-methyl-*cis*-9-decalinols. We also disclose our results on the cyclization of a chiral keto-epoxide yielding enantiomerically enriched 10-methyl-*cis*-9-decalinol.

2. Results and discussion

Our study started first with the synthesis of our model keto-epoxide **6a** bearing an electron rich arene moiety (Scheme 1, Eq. 1). This compound was prepared in 87% yield by epoxidation of the functionalized 3-methylcyclohexen-2-one **8**[20] using standard conditions with *m*-CPBA[22] in dichloromethane. We next studied the cyclization of **6a** under the influence of $SnCl_4$, known to promote the carbocyclization of keto-epoxides.[19a,b] However, the preliminary assays performed at −20 °C for 2 h (Eq. 2) led to the formation of a mixture of three compounds in a 1:1:1.2 ratio, among which the expected product (±)-**2**, the cyclopentenone contraction product (±)-**9** due to 1,2-carbonyl migration[23] and chlorohydrine (±)-**10** (*syn*/*anti*=100:0) issued from the nucleophilic addition of a chlorine ion on the tertiary carbocation intermediate. The desired 10-methyl-*cis*-9-decalinol (±)-**2** was obtained as the single cis diastereoisomer in 30% of yield, and no traces of the trans isomer was detected by ^{1}H NMR spectrometry. The stereochemistry of the product was further confirmed unambiguously by X-ray crystal structure analysis.[24] In the light of these preliminary results, even though the epoxide opening was regioselective, the reaction was not chemoselective, and the next goal was to find better conditions that would avoid the formation of the contraction product (±)-**9** as well as the unwanted chlorohydrine (±)-**10**.

The cyclization was then envisioned with $BF_3{\cdot}Et_2O$, another Lewis acid having ligands with lower nucleophilic character, in order to avoid formation of (±)-**10**. However, in these conditions (DCM, −20 °C, 2 h), the reaction afforded the undesired cyclopentenone (±)-**9** as the major product in 68% of isolated yield, along with *cis*-(±)-**2** (32%, Eq. 3). These preliminary assays confirmed the intrinsic regio- and chemoselectivities generally encountered for keto-epoxides under the influence of Lewis acids. Overall, the reactivity of such substrates appeared to be quite difficult to control and the need to find suitable conditions, that would favour selectively the cyclization product (±)-**2** over the two identified by-products, was our next goal. It appeared that this important reaction is largely undeveloped and that more reactive and discriminating catalysts or reagents are needed to address this unsolved problem in the field. In view of the reactivity of $BF_3{\cdot}Et_2O$, that avoided the formation of chlorohydrine (±)-**10**, we tried to improve these conditions in order to obtain the *cis*-9-decalinol (±)-**2** as the major product.

The influence of the solvent nature (tetrahydrofuran, nitromethane, acetonitrile, dichloromethane and 1,2-dichloroethane) on the chemoselectivity as well as the temperature (from −20 °C to 50 °C and 90 °C under microwave irradiation) were first evaluated (See Supplementary data). In our best case, the use of DCE, a low polarity solvent, at room temperature with $BF_3{\cdot}Et_2O$ (1.05 equiv) afforded almost a 1:1 ratio for cyclized product *cis*-(±)-**2** (48%) and contraction product (±)-**9** (52%). Next, the fine-tuning of the conditions in order to promote the cyclization compared to the ring contraction led us to the screening of Lewis acids in DCE as solvent and at room temperature for 2 h (Table 1). It has been reported that the strength of the Lewis acid has a crucial influence on the chemoselectivity: the weaker the Lewis acid, the more ring contraction product was formed.[19b] Experimentally, all the reactions proceeded quite well and in most cases, high conversions were observed except for $Tl(OCOCF_3)_3$, $AuCl_3$, TMSOTf and $Yb(OTf)_3$ (entries 1–4).

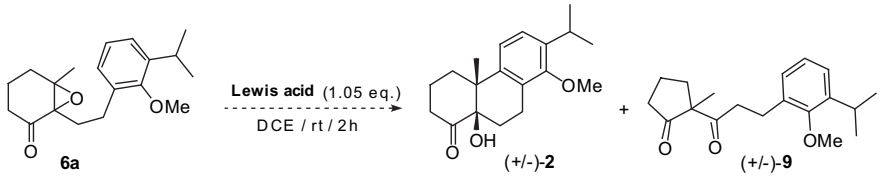


Scheme 1. Synthesis of keto-epoxide **6a** and preliminary cyclization results.

Among these four promoters, $AuCl_3$ was the most selective one and afforded a good yield (61%) of *cis*-(±)-**2**, for a conversion of 70% (entry 2). In contrast, the more oxophilic TMSOTf gave a reversed chemoselectivity towards the unwanted ring contraction product (±)-**9** in 60% yield (entry 3). When the reaction was carried out with $FeCl_3$, $Ga(OTf)_3$ and $In(OTf)_3$, quantitative conversions were observed affording almost a 1:1 to 3:2 ratios for products (±)-**2** and (±)-**9** (entries 5–7).

$TiCl_4$ permitted to obtain a 7:3 ratio for (±)-**2** and (±)-**9**, $ZrCl_4$ provided the highest selectivity (>9:1) (entries 9–11). With this promoter, 88% of *cis*-(±)-**2** was formed along with only 3% of the undesired contraction product (±)-**9** (entry 11). To our delight, the conversion of **6a** was further enhanced when the reaction was executed in DCM at room temperature and the cyclized product could be obtained with an excellent yield of 96% (entry 12). Finally, under the optimum reaction conditions, *cis*-(±)-**2** was isolated after

Table 1
Influence of the Lewis acid on the chemoselectivity for the cyclization of **6a**



Entry	Lewis acid	Conversion **6a**[a] (%)	Yield (±)-**2**[a] (%)	Yield (±)-**9**[a] (%)
1	$Tl(OCOCF_3)_3$	37	22	12
2	$AuCl_3$	70	61	8
3	TMSOTf	62	—	60
4	$Yb(OTf)_3$	16	10	3
5	$FeCl_3$	100	55	43
6	$Ga(OTf)_3$	96	57	36
7	$In(OTf)_3$	100	60	40
8	$BF_3 \cdot Et_2O$	100	58	42
9	$AlCl_3$	100	68	28
10	$TiCl_4$	100	73	25
11	$ZrCl_4$	91	88	3
12	$ZrCl_4$[b]	100	96 (90[c])	3

[a] Conversion and yield evaluated by HPLC analysis.
[b] DCM was used as solvent.
[c] Isolated yield.

This selectivity is however comparable with the one first obtained with $BF_3 \cdot Et_2O$ (entry 8). Reacting **6a** with harder oxophilic Lewis acids, such as $AlCl_3$, $TiCl_4$ and $ZrCl_4$ favoured the formation of 10-methyl-*cis*-9-decalinol (±)-**2**. Indeed, while the use of $AlCl_3$ and purification on column chromatography on silica gel with an excellent 90% yield. Control experiments carried out with stoichiometric and catalytic amounts of HCl in DCM were unsatisfactory, suggesting that the unsurpassed observed chemoselectivity and

efficiency of the reaction for the cyclization pathway is ascribed to the unique activation mode of $ZrCl_4$ alone, and not to any residual traces of HCl. It is worth to mention that, in strictly the same experimental conditions, the use of AgOTf, $Sc(OTf)_3$, $CuSO_4$ or $Co(acac)_3$ was unsuccessful. Attempts to cyclize **6a** with other zirconium salts, such as ZrF_4 or $Zr(OEt)_4$ was ineffective (unreactive), except when $ZrBr_4$ was employed. In this case, *cis*-(±)-**2** was formed in good yield (88%) without alteration of the diastereoselectivity (see SD).

The observed exclusive *cis*-stereochemistry preference is rationalized as shown in Fig. 3.

Under the influence of $ZrCl_4$, the epoxide opens regioselectively providing the α-hydroxyketone carbocation intermediate **11**. Due to the strength of the Zr(IV)–O bonds, the metal cation binds tightly to the generated α-hydroxyketone via a stable five-membered ring.[25] It is assumed that the formation of this stable bidentic chelate **11** avoids the carbonyl migration, and therefore the C–C bond breaking responsible for the competitive contraction process. Then, nucleophilic pseudo-axial attack (from the α-face) of the arene onto the carbocation species provides the *cis*-decalinol junction **12**, which upon hydrolysis affords *cis*-(±)-**2** highly diastereoselectively. Cyclization proceeding through equally unfavourable pathway (from the β-face) would provide the other trans-diastereoisomer, which was not observed. It is postulated that the Zr(IV) complex **11** involved during the cyclization accounts for the unrivalled efficiency and chemoselectivity of the transformation. The high bond dissociation energy (BDE) of Zr(IV)–O bond might also be one of the main reasons that do not permit the use of a catalytic amount of $ZrCl_4$. Indeed, attempts to use a catalytic amount of the promoter were unsuccessful and this is most likely due to the turnover blockage of Zr(IV) held tightly within intermediate **12**.

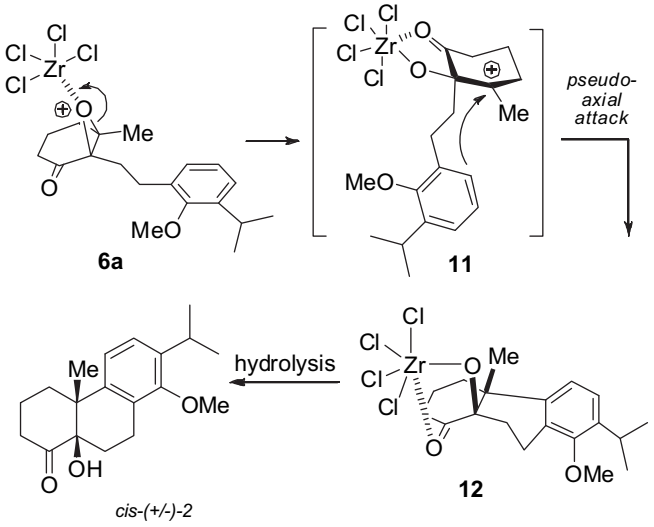
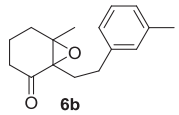
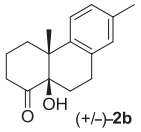
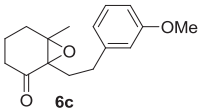
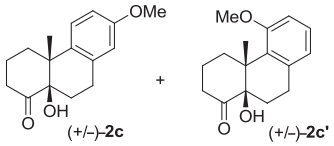
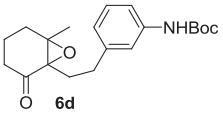
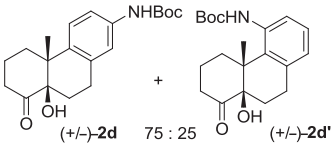
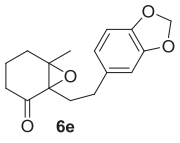
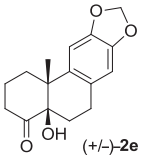
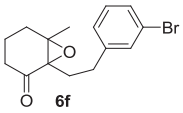
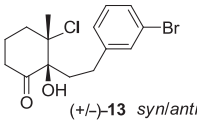
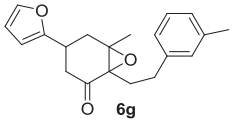
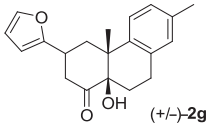
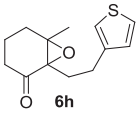
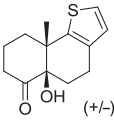
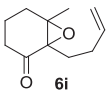
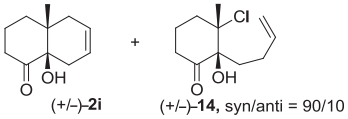
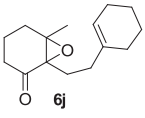
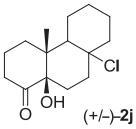
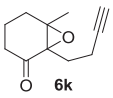
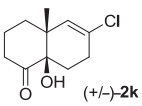
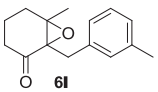
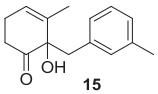
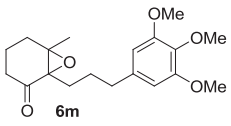
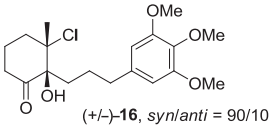


Fig. 3. Proposed mechanism for the $ZrCl_4$-promoted cationic cyclization of keto-epoxide **6a**.

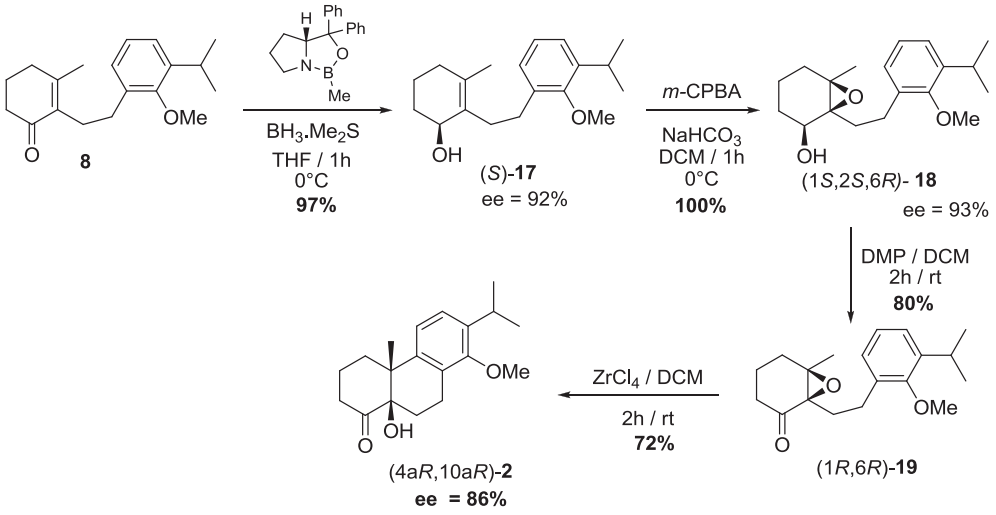
Having rationalized the cis-stereochemistry, we were then interested in studying the scope and limitation of this new $ZrCl_4$-promoted procedure. The optimized conditions were applied to a large panel of keto-epoxides bearing electron rich and electron-deficient arenes, thiophene, terminal alkene and alkyne, and a trisubstituted olefin (Table 2). Keto-epoxides of interest (**6b**–**m**) were synthesized either by *m*-CPBA or by hydrogen peroxide epoxidations of the corresponding C2-substituted 3-methylcyclohexenones, most of which have been already described by our laboratory recently.[21,26] Results confirmed that the cyclization of keto-epoxides bearing electron-donating substituents on the arene moiety proceeded well under the influence of $ZrCl_4$. Indeed, substrates **6b**, **6c**, **6d** and **6e** gave rise to the expected 10-methyl-*cis*-9-decalinols in good to excellent isolated yields, in the range of 74–90% (Table 2, entries 1–4). It is important to mention that (±)-**2b** was obtained as a single regioisomer and the electrophilic substitution did not involve the *ortho* position of the aromatic ring (entry 1). In the case of substrates **6c** and **6d**, possessing a methoxy group and a protected amine, respectively, two regioisomers were obtained resulting from the addition of the arene either on the *ortho* or on the *para* position, the *para* substitution being the most favourable in both cases (entries 2 and 3). Whereas (±)-**2c** (57%) and (±)-**2c′** (34%) could easily be separated by column chromatography on silica gel, decalinols (±)-**2d** and (±)-**2d′** were obtained as an inseparable mixture in a 75:25 ratio. Compared to literature report,[19b] the 3:2 ratio observed for (±)-**2c**/(±)-**2c′** is different and slightly higher than the one obtained by Sutherland (1:1 ratio), for the same substrate however upon $BF_3 \cdot Et_2O$ or $SnCl_4$ activations (entry 2). On the opposite, keto-epoxide **6f** having an electron-deficient arene gave the chlorohydrine (±)-**13**, as the sole reaction product in 88% of yield with a *syn*/*anti* ratio of 63:37 (entry 5). This undesired pathway is likely the most favored kinetically in these conditions for substrates bearing electron-deficient arenes. Interestingly, substituents on the cyclohexenone moiety did not affect the efficiency, chemo- and diastereoselectivity of the cyclization. Indeed, 10-methyl-*cis*-9-decalinol (±)-**2g** was obtained highly selectively from keto-epoxide **6g** exhibiting a furanyl substituent, with a satisfactorily 77% yield (entry 6). Results also demonstrated the possibility to modulate the nature of the internal nucleophile. A versatile functional group, such as thiophene is tolerated and permitted the cyclization event to occur regioselectively at the C2-position of the heteroaromatic ring. Compound (±)-**2h** was successfully isolated in a very good 86% yield (entry 7). Cyclizations of keto-epoxides featuring olefins and terminal alkyne were also studied by reacting substrates **6i**, **6j** and **6k** (entries 8–10). Subjecting **6i** under the optimized conditions gave rise to the formation of the desired *cis*-decalinol (±)-**2i** in 52% of yield along with 20% of chlorohydrine (±)-**14** (*syn*/*anti* ratio 90:10) due to a low nucleophilic unactivated terminal olefin (entry 8). In the case of the more electron rich trisubstituted olefin **6j**, the cyclization led to the chlorinated tricyclic system (±)-**2j** in satisfactory yield (66%), accompanied with other complex unidentified by-products (entry 9). The quaternary chlorinated carbon centre is most likely generated during the termination step between the tertiary carbocation intermediate and Cl^-. Keto-epoxide bearing a terminal alkyne confirmed to be an excellent substrate for the reaction. Indeed, submitting **6k** to the optimal conditions permitted the selective access to the chlorinated trisubstituted olefin 10-methyl-*cis*-9-decalinol (±)-**2k** in excellent 89% yield (entry 10) and in agreement with Sutherland's report (using $BF_3 \cdot Et_2O$ or $TiCl_4$).[19c] Additionally, we also envisioned the possibility of synthesizing C5- and C7-membered fused rings by cyclization of keto-epoxides **6l** and **6m** (entries 11 and 12). Unfortunately, the desired reaction did not occur in both cases most likely due to high energy transition states. Instead, the allylic alcohol **15**, arising from HCl elimination on the corresponding chlorohydrine, and product (±)-**16** (*syn*/*anti* ratio 90:10) were formed in quite high yields (74% each).

Finally, we decided to evaluate whether our $ZrCl_4$ cyclization conditions could be applied to chiral keto-epoxide (1*R*,6*R*)-**19** without alteration of the chiral centres. Accordingly, substrate **19** was synthesized in three steps from the parent compound **8** (Scheme 2). The α,β-unsaturated ketone **8** was first reduced enantioselectively using Corey's oxazaborolidine[27] giving rise to allylic alcohol (*S*)-**17** in 97% of yield with an enantiomeric excess of 92%, in agreement with Corey's report.[28] Subsequent diastereoselective epoxidation of (*S*)-**17** by *m*-CPBA in the presence of sodium hydrogenocarbonate afforded epoxy-alcohol (1*S*,2*S*,6*R*)-**18** quantitatively in diastereoisomeric ratio >99:1, and the enantiomeric excess was determined to be 93%.

Table 2
Cationic cyclization of various keto-epoxides[a]

Entry	Keto-epoxide	Product	Yield[b] (%)
1	 **6b**	 (+/–)-**2b**	90
2	 **6c**	 (+/–)-**2c** + (+/–)-**2c'**	57+34
3	 **6d**	 (+/–)-**2d** 75 : 25 (+/–)-**2d'**	74
4	 **6e**	 (+/–)-**2e**	89
5	 **6f**	 (+/–)-**13** *syn*/*anti* : 63/37	88
6	 **6g**	 (+/–)-**2g**	77
7	 **6h**	 (+/–)-**2h**	86
8	 **6i**	 (+/–)-**2i** + (+/–)-**14,** syn/anti = 90/10	52+20
9	 **6j**	 (+/–)-**2j**	66
10	 **6k**	 (+/–)-**2k**	89
11	 **6l**	 **15**	74
12	 **6m**	 (+/–)-**16**, *syn*/*anti* = 90/10	74

[a] Conditions: $ZrCl_4$ (1.05 equiv), DCM, 2 h, room temperature.
[b] Isolated yield.



Scheme 2. Assay for the cyclization of chiral keto-epoxide (1*R*,6*R*)-**19**.

Oxidation of the secondary alcohol using Dess–Martin periodinane allowed the preparation of the desired chiral (1*R*,6*R*)-**19** in 80% of yield. Cyclization conditions applied to keto-epoxide **19** afforded successfully chiral 10-methyl-*cis*-9-decalinol (4a*R*,10a*R*)-**2** with a satisfactory enantiomeric excess (*ee* 86%). This preliminary result, which has to be further optimized, highlights the compatibility of our $ZrCl_4$-promoted cationic cyclization with chiral keto-epoxide, expanding the scope of application of this reaction.

3. Conclusion

In summary, we have developed an efficient $ZrCl_4$-promoted cationic cyclization of keto-epoxides for the diastereoselective preparation of 10-methyl-*cis*-9-decalinols, an important structural motif encountered in numerous natural products. Key for this highly diastereoselective cyclization is the use of a zirconium based Lewis acid, which permits to induce good reactivity and diastereoselectivity compared to other promoters. This cationic cyclization appears to be quite general and tolerates many internal nucleophiles, such as arenes, thiophene, alkene and alkyne. The newly developed methodology allows also the cyclization of a chiral keto-epoxide with good enantiomeric excess. Further developments and optimization of this enantiomeric cyclization is underway in our laboratory and will be reported in due course, as well as mechanistical investigations.

4. Experimental

4.1. General

All reagents were purchased from Sigma–Aldrich, ABCR, Alfa-Aesar and Acros and were used as received. NMR spectra were recorded on a Brucker Advance 400 (400 MHz ^{1}H NMR, 100 MHz ^{13}C NMR) in $CDCl_3$. Chemical shift values (δ) are reported in parts per million (residual chloroform δ=7.26 ppm for ^{1}H; residual chloroform δ=77.16 ppm for ^{13}C). Infra-red spectra were recorded with a Nicolet 380 FT-IR apparatus. High resolution mass spectra were recorded with an Agilent Q-Tof 6520 apparatus equipped with a positive ESI source.

4.2. General procedure for the synthesis of keto-epoxides by *m*-CPBA epoxidation (method A)

m-CPBA (1.40 mmol, 2.0 equiv) was added to a solution of the corresponding C2-substituted 3-methylcyclohexenones[21,26] (0.698 mmol, 1.0 equiv) in dichloromethane (6 mL) and the reaction mixture was stirred for 20 h at room temperature. Then, after dilution with dichloromethane (20 mL), the residue was washed with saturated aqueous sodium hydrogenocarbonate (10 mL) and brine (10 mL). The combined organic extracts were dried over sodium sulfate and evaporated. The residue was purified by chromatography on silica gel (eluent: cyclohexane/ethyl acetate) to give the keto-epoxide derivatives **6a**–**f** and **6l**.

*4.2.1. 1-[2-(3-Isopropyl-2-methoxyphenyl)ethyl]-6-methyl-7-oxabicyclo[4.1.0]heptan-2-one (**6a**).* White solid; R_f=0.68 (cyclohexane/EtOAc 80:20); mp 46–47 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.01 (m, 3H), 3.69 (s, 3H), 3.23 (hept., *J*=6.8 Hz, 1H), 2.19 (m, 4H), 1.56 (m, 7H), 1.21 (dd, *J*=6.8, 1.2 Hz, 6H), 0.95 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=206.1, 155.7, 142.1, 134.6, 128.3, 125.0, 124.7, 66.2, 65.9, 61.4, 37.1, 30.1, 28.2, 26.4, 26.3, 24.3, 24.2, 19.4, 17.3 ppm; IR (neat): ν=2960, 1704, 1463, 1428, 1406, 1382, 1253, 1202, 1167, 1046, 1010, 783, 765 cm^{-1}; HRMS (ESI, *m*/*z*): calcd for $C_{19}H_{26}O_3$ $[M+H]^+$, 303.1960; found, 303.1959.

*4.2.2. 6-Methyl-1-[2-(3-methylphenyl)ethyl]-7-oxabicyclo[4.1.0]heptan-2-one (**6b**).* Colourless oil; R_f=0.45 (cyclohexane/EtOAc 80:20); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.15 (t, *J*=7.6 Hz, 1H), 6.98 (m, 3H), 2.54 (m, 3H), 2.34 (m, 1H), 2.33 (s, 3H), 2.02 (m, 2H), 1.83 (m, 3H), 1.59 (m, 1H), 1.30 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=206.7, 141.6, 138.0, 129.4, 128.4, 126.9, 125.6, 66.7, 66.4, 37.2, 31.5, 30.1, 28.5, 21.5, 19.9, 17.7 ppm; IR (neat): ν=2940, 1705, 1609, 1455, 1381, 1156, 1119, 1046, 912, 778, 702 cm^{-1}; HRMS (ESI, *m*/*z*): calcd for $C_{16}H_{20}O_2$ $[M+H]^+$, 245.1542; found, 245.1538.

*4.2.3. 1-[2-(3-Methoxyphenyl)ethyl]-6-methyl-7-oxabicyclo[4.1.0]heptan-2-one (**6c**).* Yellow oil; R_f=0.52 (cyclohexane/EtOAc 80:20); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.18 (dd, *J*=7.6, 8.8 Hz, 1H), 6.73 (m, 3H), 3.80 (s, 3H), 2.54 (m, 3H), 2.32 (m, 1H), 2.03 (m, 2H), 1.84 (m, 3H), 1.58 (m, 1H), 1.32 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=206.7, 159.8, 143.3, 129.4, 121.0, 114.3, 111.5, 66.6, 66.5, 55.3, 37.1, 31.7, 30.1, 28.4, 19.9, 17.6 ppm; IR (neat): ν=2938, 1705, 1601, 1585, 1489, 1456, 1436, 1258, 1153, 1040, 781, 698 cm^{-1}; HRMS (ESI, *m*/*z*): calcd for $C_{16}H_{20}O_3$ $[M+Na]^+$, 283.1310; found, 283.1296.

*4.2.4. tert-Butyl{3-[2-(6-methyl-2-oxo-7-oxabicyclo[4.1.0]hept-1-yl)ethyl]phenyl} carbamate (**6d**).* Red oil; R_f=0.61 (cyclohexane/EtOAc 70:30); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.22 (s, 1H), 7.14 (m, 2H), 6.84 (dt, *J*=1.6, 6.8 Hz, 1H), 6.52 (s, 1H), 2.63 (m, 2H), 2.52 (m, 1H), 2.32

(m, 1H), 2.02 (m, 2H), 1.840 (m, 3H), 1.50 (s, 9H), 1.27 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=206.6, 152.8, 142.7, 138.5, 129.0, 123.3, 118.6, 116.3, 80.5, 66.5, 66.4, 37.1, 31.6, 30.0, 28.4, 28.3, 19.8, 17.6 ppm; IR (neat): ν=2984, 2968, 1712, 1603, 1567, 1468, 1452, 1223, 1161, 1094, 954, 851, 774, 695 cm^{-1}; HRMS (ESI, *m*/*z*): calcd for $C_{20}H_{27}NO_4$ $[M+H]^+$, 346.2018; found, 346.2013.

*4.2.5. 1-[2-(1,3-Benzodioxol-5-yl)ethyl]-6-methyl-7-oxabicyclo[4.1.0] heptan-2-one (**6e**).* Colourless oil; R_f=0.73 (cyclohexane/EtOAc 60:40); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.68 (m, 2H), 6.61 (dd, *J*=1.6, 7.6 Hz, 1H), 5.91 (s, 2H), 2.55 (m, 3H), 2.32 (m, 1H), 2.01 (m, 2H), 1.82 (m, 4H), 1.57 (m, 1H), 1.34 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=206.7, 147.7, 145.8, 135.6, 121.2, 101.1, 108.2, 100.9, 66.6, 66.4, 37.1, 31.4, 30.1, 28.7, 19.9, 17.7 ppm; IR (neat): ν=2940, 1703, 1595, 1567, 1475, 1455, 1426, 1118, 1094, 821, 779, 693 cm^{-1}; HRMS (ESI, *m*/*z*): calcd for $C_{16}H_{18}O_4$ $[M+H]^+$, 275.1283; found, 275.1579.

*4.2.6. 1-[2-(3-Bromophenyl)ethyl]-6-methyl-7-oxabicyclo[4.1.0]heptan-2-one (**6f**).* Yellow oil; R_f=0.57 (cyclohexane/EtOAc 80:20); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.31 (m, 2H), 7.11 (m, 2H), 2.66 (m, 2H), 2.54 (dt, *J*=5.6, 18.0 Hz, 1H), 2.25 (m, 1H), 2.02 (m, 2H), 1.84 (m, 3H), 1.58 (m, 1H), 1.32 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=206.7, 144.1, 131.6, 130.1, 129.2, 127.3, 122.5, 66.6, 66.5, 37.0, 31.3, 30.0, 28.2, 19.9, 17.6 ppm; IR (neat): ν=2954, 1645, 1614, 1451, 1368, 1296, 1234, 1147, 1072, 774, 700 cm^{-1}; HRMS (ESI, *m*/*z*): calcd for $C_{15}H_{17}BrO_2$ $[M+NH_4]^+$, 326.0756; found, 326.0757.

*4.2.7. 6-Methyl-1-(3-methylbenzyl)-7-oxabicyclo[4.1.0]heptan-2-one (**6l**).* Colourless oil; R_f=0.55 (cyclohexane/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.05 (t, *J*=7.6 Hz, 1H), 6.89 (m, 3H), 3.36 (d, *J*=14.8 Hz, 1H), 2.84 (d, *J*=14.8 Hz, 2H), 2.43 (td, *J*=4.0, 16.8 Hz, 1H), 2.24 (s, 3H), 2.06 (m, 1H), 1.77 (m, 3H), 1.50 (m, 1H), 1.46 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=206.1, 138.0, 136.8, 130.0, 128.3, 127.1, 126.0, 66.9, 66.4, 37.3, 31.8, 30.2, 21.5, 20.5, 17.6 ppm; IR (neat): ν=2942, 1707, 1607, 1489, 1454, 1382, 1174, 1117, 1039, 931, 748, 693 cm^{-1}; HRMS (ESI, *m*/*z*): calcd for $C_{15}H_{18}O_2$ $[M+H]^+$, 231.1385; found, 231.1381.

4.3. General procedure for the synthesis of keto-epoxides by H_2O_2 epoxidation (method B)

Hydrogen peroxide 30% aq (3.0 mmol, 3.0 equiv) and an aqueous solution of sodium hydroxide 6 N (3.0 mmol, 3.0 equiv) were added to a solution of the corresponding C2-substituted 3-methylcyclohexenones[21,26] (1.0 mmol, 1.0 equiv) in methanol (10 mL) at 0 °C. After being stirred for 30 min at 0 °C, the reaction mixture was stirred at room temperature 3 h before a second addition of H_2O_2 30% (3.0 mmol, 3.0 equiv) and aqueous NaOH 6 N (3.0 mmol, 3.0 equiv). The reaction mixture was stirred overnight, then saturated sodium sulfite (12 mL) and water (12 mL) were added. The aqueous phase was extracted by diethyl ether (3×30 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated. The residue was purified by chromatography on silica gel (eluent: cyclohexane/ethyl acetate) to give the keto-epoxide derivatives **6g**–**k** and **6m**.

*4.3.1. 4-(2-Furyl)-6-methyl-1-[2-(3-methylphenyl)ethyl]-7-oxabicyclo[4.1.0]heptan-2-one (**6g**).* Orange oil; R_f=0.40 (cyclohexane/EtOAc 90:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.18 (dd, *J*=0.8, 2.0 Hz, 1H), 7.17 (t, *J*=7.6 Hz, 1H), 6.98 (m, 3H), 6.29 (dd, *J*=2.0, 3.2 Hz, 1H), 6.00 (dt, *J*=0.8, 3.2 Hz, 1H), 3.37 (m, 1H), 2.79 (ddd, *J*=1.6, 5.2, 18.0 Hz, 1H), 2.57 (m, 3H), 2.45 (m, 1H), 2.39 (m, 1H), 2.34 (s, 3H), 2.04 (dd, *J*=11.6, 14.8 Hz, 1H), 1.80 (m, 1H), 1.34 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.5, 156.6, 141.6, 141.4, 138.1, 129.4, 128.4, 126.9, 125.6, 110.2, 104.5, 65.9, 65.1, 41.9, 35.5, 31.5, 28.6, 28.5, 21.5, 19.6 ppm; IR (neat): ν=2930, 1709, 1608, 1507, 1454, 1381, 1147, 1114, 1061, 1013, 928, 781, 736, 703 cm^{-1}; HRMS (ESI, *m*/*z*): calcd for $C_{20}H_{22}O_3$ $[M+H]^+$, 311.1647; found, 311.1642.

*4.3.2. 6-Methyl-1-[2-(3-thienyl)ethyl]-7-oxabicyclo[4.1.0]heptan-2-one (**6h**).* Yellow oil; R_f=0.42 (cyclohexane/EtOAc 80:20); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.23 (t, *J*=3.6 Hz, 1H), 6.93 (d, *J*=4.0 Hz, 2H), 2.71 (m, 3H), 2.53 (dt, *J*=5.2, 17.2 Hz, 1H), 2.31 (m, 1H), 2.00 (m, 2H), 1.85 (m, 3H), 1.59 (m, 1H), 1.34 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=206.5, 141.7, 128.2, 125.3, 120.3, 66.5, 66.3, 36.9, 29.9, 27.3, 25.8, 19.7, 17.5 ppm; IR (neat): ν=2936, 1742, 1623, 1591, 1555, 1474, 1450, 1421, 1127, 1040, 821, 780, 693 cm^{-1}; HRMS (ESI, *m*/*z*): calcd for $C_{13}H_{16}O_2S$ $[M+H]^+$, 237.0949; found, 237.0944.

*4.3.3. 1-But-3-en-1-yl-6-methyl-7-oxabicyclo[4.1.0]heptan-2-one (**6i**).* Colourless oil; R_f=0.55 (cyclohexane/EtOAc 90:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.75 (m, 1H), 4.98 (m, 1H), 4.93 (m, 1H), 2.51 (td, *J*=4.0, 17.2 Hz, 1H), 1.99 (m, 5H), 1.83 (m, 2H), 1.65 (m, 1H), 1.55 (m, 1H), 1.44 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=206.6, 138.0, 114.9, 66.7, 66.1, 37.1, 30.2, 29.6, 25.6, 20.1, 17.7 ppm; IR (neat): ν=2940, 1706, 1641, 1454, 1382, 1328, 1113, 997, 912, 825 cm^{-1}; HRMS (ESI, *m*/*z*): calcd for $C_{11}H_{16}O_2$ $[M+H]^+$, 181.1229; found, 181.1126.

*4.3.4. 1-(2-Cyclohex-1-en-1-ylethyl)-6-methyl-7-oxabicyclo[4.1.0] heptan-2-one (**6j**).* Colourless oil; R_f=0.52 (cyclohexane/EtOAc 90:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.38 (br, 1H), 2.49 (td, *J*=4.4, 17.2 Hz, 1H), 2.01 (m, 1H), 1.83 (m, 10H), 1.50 (m, 6H), 1.44 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=206.2, 137.3, 121.4, 66.9, 65.9, 37.1, 33.5, 30.2, 28.3, 25.3, 24.9, 23.0, 22.5, 20.0, 17.6 ppm; IR (neat): ν=2925, 2856, 2835, 1706, 1451, 1439, 1381, 1134, 914, 833 cm^{-1}; HRMS (ESI, *m*/*z*): calcd for $C_{15}H_{22}O_2$ $[M+NH_4]^+$, 252.1964; found, 252.1960.

*4.3.5. 1-But-3-yn-1-yl-6-methyl-7-oxabicyclo[4.1.0]heptan-2-one (**6k**).* Colourless oil; R_f=0.50 (cyclohexane/EtOAc 70:30); ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.50 (td, *J*=4.0, 16.8 Hz, 1H), 2.31 (m, 2H), 2.19 (m, 1H), 2.03 (m, 2H), 1.85 (m, 4H), 1.56 (m, 1H), 1.48 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=206.3, 83.6, 69.0, 66.6, 65.9, 37.0, 30.1, 25.2, 20.3, 17.5, 14.6 ppm; IR (neat): ν=2946, 1658, 1631, 1420, 1368, 1342, 1323, 1181, 1139, 1112, 1059, 631 cm^{-1}; HRMS (ESI, *m*/*z*): calcd for $C_{11}H_{14}O_2$ $[M+H]^+$, 179.1072; found, 179.1068.

*4.3.6. 6-Methyl-1-[3-(3,4,5-trimethoxyphenyl)propyl]-7-oxabicyclo [4.1.0]heptan-2-one (**6m**).* Colourless oil; R_f=0.21 (cyclohexane/EtOAc 80:20); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.40 (s, 2H), 3.84 (s, 6H), 3.80 (s, 3H), 2.50 (m, 3H), 1.97 (m, 3H), 1.83 (m, 2H), 1.55 (m, 4H), 1.40 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=207.0, 153.1, 137.8, 136.2, 105.3, 67.1, 66.3, 60.9, 51.1, 37.0, 36.5, 30.0, 29.9, 19.9, 17.7 ppm; IR (neat): ν=2939, 1704, 1588, 1508, 1456, 1420, 1341, 1238, 1126, 1011, 827 cm^{-1}; HRMS (ESI, *m*/*z*): calcd for $C_{19}H_{26}O_5$ $[M+H]^+$, 335.1859; found, 335.1859.

4.4. *cis*-10a-Hydroxy-7-isopropyl-8-methoxy-4a-methyl-3,4,4a,9,10,10a-hexahydrophenanthren-1(2*H*)-one ((±)-2) under $ZrCl_4$ conditions

Zirconium tetrachloride (205 mg, 0.869 mmol, 1.05 equiv) was added to a solution of epoxide **6a** (250 mg, 0.828 mmol, 1.0 equiv) in dichloromethane (25 mL) and the reaction mixture was stirred for 2 h at room temperature. After addition of water (50 mL), the aqueous phase was extracted by diethyl ether (3×25 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated. The residue was purified by chromatography on silica gel (eluent: cyclohexane/ethyl acetate 80:20) to give (±)-**2** as a white solid (225 mg, 90%). R_f=0.48 (cyclohexane/EtOAc 80:20); mp 129–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.08

(d, J=8.4 Hz, 1H), 6.99 (d, J=8.4 Hz, 1H), 4.01 (br, 1H), 3.73 (s, 3H), 3.24 (hept., J=6.9 Hz, 1H), 1.65–3.09 (m, 10H), 1.26 (s, 3H), 1.20 (d, J=6.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=215.1, 154.6, 142.7, 138.8, 127.7, 124.4, 122.3, 79.8, 60.7, 45.8, 41.1, 36.9, 29.7, 26.3, 24.0, 22.6, 20.8, 19.9 ppm; IR (neat): ν=3473, 2960, 1706, 1462, 1412, 1330, 1251, 1119, 1087, 1063, 1036, 1012, 967, 931, 814 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{19}H_{26}O_3$ $[M+H]^+$, 303.1960; found, 303.1959.

Using the same procedure, chiral (4a*R*,10a*R*)-**2** was prepared from (1*R*,6*R*)-**19** (50 mg, 0.165 mmol). Compound (4a*R*,10a*R*)-**2** was thus obtained as a white paste (36 mg, 72%) with an enantiomeric excess of 86%. $[\alpha]_D^{24}$ +12.1 (*c* 1 M, MeOH).

4.5. 2-[3-(3-Isopropyl-2-methoxyphenyl)propanoyl]-2-methyl cyclopentanone ((±)-9) and 3-chloro-2-hydroxy-2-[2-(3-isopropyl-2-methoxyphenyl)ethyl]-3-methylcyclohexanone ((±)-10) under $SnCl_4$ conditions

Tin(IV) chloride (37 μL, 0.348 mmol, 1.05 equiv) was added to a solution of epoxide **6a** (100 mg, 0.331 mmol, 1.0 equiv) in dichloromethane (10 mL) at −20 °C and the reaction mixture was stirred for 2 h at this temperature. After addition of water (20 mL), the aqueous phase was extracted by diethyl ether (3×20 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated. The residue was purified by chromatography on silica gel (eluent: cyclohexane/ethyl acetate 90:10) yielding three clean products: (±)-**2** as a white solid (30 mg, 30%), (±)-**9** as a white solid (29 mg, 29%) and (±)-**10** as a pale white solid (42 mg, 37%). Analysis of (±)-**9**: R_f=0.61 (cyclohexane/EtOAc 80:20); mp 50–51 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.95 (m, 3H), 3.73 (s, 3H), 3.22 (hept., J=6.8 Hz, 1H), 2.86 (s, 4H), 2.52 (m, 1H), 2.24 (t, J=7.8 Hz, 2H), 1.81 (quint, J=6.8 Hz, 2H), 1.59 (m, 1H), 1.30 (s, 3H), 1.21 (d, J=6.8 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=217.0, 207.5, 155.7, 142.2, 133.9, 127.7, 125.1, 124.5, 63.6, 61.7, 39.2, 38.1, 34.3, 26.4, 24.9, 24.1, 20.3, 19.4 ppm; IR (neat): ν=2962, 1737, 1701, 1461, 1428, 1252, 1202,1166, 1097, 1051, 1010, 797, 766 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{19}H_{26}O_3$ $[M+H]^+$, 303.1960; found, 303.1961. Analysis of (±)-**10**: R_f=0.73 (cyclohexane/EtOAc 80:20); mp 97–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.13 (dd, J_1=2.1 Hz, J_2=7.5 Hz, 1H), 7.02 (t, J=7.5 Hz, 1H), 6.97 (dd, J_1=2.1 Hz, J_2=7.5 Hz, 1H), 3.95 (s, 1H), 3.69 (s, 3H), 3.24 (hept., J=6.6 Hz, 1H), 2.55 (m, 3H), 1.92 (m, 7H), 1.68 (s, 3H), 1.24 (t, J=6.6 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=210.9, 155.6, 142.3, 134.1, 127.9, 125.4, 124.8, 83.5, 82.2, 61.9, 37.6, 36.7, 36.1, 26.4, 26.3, 25.2, 24.4, 24.1, 22.5 ppm; IR (neat): ν=3490, 2961, 1719, 1460, 1428, 1314, 1255, 1202, 1173, 1122, 1114, 1078, 1050, 1008, 840, 799, 766, 607, 533 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{19}H_{27}ClO_3$ $[M+H]^+$, 338.1649; found, 338,1652.

4.6. *cis*-10a-Hydroxy-7-isopropyl-8-methoxy-4a-methyl-3,4,4a,9,10,10a-hexahydrophenanthren-1(2*H*)-one ((±)-2b)

cis-9-Decalinol (±)-**2b** was obtained using the same procedure as for the synthesis of (±)-**2** with keto-epoxide **6b** (45 mg, 0.183 mmol). Purification by chromatography on silica gel (eluent: cyclohexane/ethyl acetate 80:20) gave (±)-**2b** as a white solid (41 mg, 90%). R_f=0.25 (cyclohexane/EtOAc 80:20); mp 79–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.13 (d, J=8.0 Hz, 1H), 6.99 (d, J=8.0 Hz, 1H), 6.95 (s, 1H), 3.99 (s, 1H), 3.18 (m, 1H), 2.69 (dd, J_1=6.0 Hz, J_2=18.0 Hz, 1H), 2.53 (m, 1H), 2.41 (qd, J_1=2.4 Hz, J_2=14.0 Hz, 1H), 2.30 (m, 1H), 2.21 (s, 3H), 1.96 (dd, J_1=4.0 Hz, J_2=13.6 Hz, 1H), 1.82 (m, 2H), 1.72 (m, 1H), 1.52 (m, 1H), 1.26 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=214.9, 140.9, 135.4, 133.8, 129.6, 127.3, 126.2, 80.1, 45.5, 41.1, 36.9, 29.9, 25.6, 22.5, 20.9, 20.6 ppm; IR (neat): ν=3471, 2921, 1702, 1499, 1448, 1428, 1380, 1311, 1247, 1226, 1151, 1119, 1087, 1057, 964, 937, 812 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{16}H_{20}O_2$ $[M+H]^+$, 245.1542; found, 245.1546.

4.7. *cis*-10a-Hydroxy-7-methoxy-4a-methyl-3,4,4a,9,10,10a-hex ahydrophenanthren-1(2*H*)-one ((±)-2c) and *cis*-10a-hydroxy-5-methoxy-4a-methyl-3,4,4a,9,10,10a-hexahydrophenanthren-1(2*H*)-one ((±)-2c′)

cis-9-Decalinols (±)-**2c** and (±)-**2c′** were obtained using the same procedure as for the synthesis of (±)-**2** with keto-epoxide **6c** (50 mg, 0.192 mmol). Purification by chromatography on silica gel (eluent: cyclohexane/ethyl acetate 90:10) gave (±)-**2c** as a colourless solid (29 mg, 57%) and (±)-**2c′** as a colourless solid (17 mg, 34%). Experimental data for (±)-**2c** and (±)-**2c′** were identical to the data reported in the literature.[19a]

4.8. *tert*-Butyl(8a-hydroxy-4b-methyl-8-oxo-4b,5,6,7,8,8a,9,10-octahydrophenanthren-4-yl)carbamate ((±)-2d) and *tert*-butyl(8a-hydroxy-4b-methyl-8-oxo-4b,5,6,7,8,8a,9,10-octahyd rophenanthren-2-yl)carbamate ((±)-2d′)

cis-9-Decalinols (±)-**2d** and (±)-**2d′** were obtained using the same procedure as for the synthesis of (±)-**2** with keto-epoxide **6d** (50 mg, 0.145 mmol). Purification by chromatography on silica gel (eluent: cyclohexane/ethyl acetate 90:10) gave an inseparable mixture of (±)-**2d** and (±)-**2d′** in a 75:25 ratio (37 mg, 74%). R_f=0.42 (cyclohexane/EtOAc 70:30); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.09 (s, 3.5H), 6.44 (s, 0.2H$_{(\pm)\text{-}\mathbf{2d'}}$), 6.38 (s, 1H$_{(\pm)\text{-}\mathbf{2d}}$), 4.00 (s, 0.2H$_{(\pm)\text{-}\mathbf{2d'}}$), 3.88 (s, 1H$_{(\pm)\text{-}\mathbf{2d}}$), 3.16 (m, 1H), 2.74 (m, 1H), 2.61 (m, 1H), 2.48 (m, 1H), 2.37 (dt, J_1=6.0 Hz, J_2=13.2 Hz, 1H), 1.88 (m, 4H), 1.76 (m, 1H), 1.52 (s, 3H$_{(\pm)\text{-}\mathbf{2d'}}$), 1.51 (s, 9H$_{(\pm)\text{-}\mathbf{2d}}$), 1.15 (s, 1H$_{(\pm)\text{-}\mathbf{2d'}}$), 1.14 (s, 3H$_{(\pm)\text{-}\mathbf{2d}}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=214.8, 153.0, 138.8, 136.1, 134.9, 129.2 ($C_{\mathbf{2d'}}$), 126.9, 123.2 ($C_{\mathbf{2d'}}$), 118.7 ($C_{\mathbf{2d}}$), 117.3 ($C_{\mathbf{2d}}$), 85.0 ($C_{\mathbf{2d'}}$), 80.5 ($C_{\mathbf{2d}}$), 80.0 ($C_{\mathbf{2d}}$), 45.4 ($C_{\mathbf{2d}}$), 41.1 ($C_{\mathbf{2d}}$), 39.3 ($C_{\mathbf{2d'}}$), 37.9 ($C_{\mathbf{2d'}}$), 36.8 ($C_{\mathbf{2d}}$), 36.7 ($C_{\mathbf{2d'}}$), 29.9 ($C_{\mathbf{2d}}$), 29.4 ($C_{\mathbf{2d'}}$), 28.5 ($C_{\mathbf{2d}}$), 25.9 ($C_{\mathbf{2d}}$), 25.2 ($C_{\mathbf{2d'}}$), 22.5 ($C_{\mathbf{2d}}$), 21.7 ($C_{\mathbf{2d'}}$), 20.6 ($C_{\mathbf{2d}}$) ppm; IR (neat): ν=3323, 2971, 1719, 1708, 1593, 1539, 1366, 1241, 1160, 1088, 1078, 1053, 967, 913 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{20}H_{27}NO_4$ $[M+H]^+$, 346.2018; found, 346.2014.

4.9. *cis*-4a-Hydroxy-11b-methyl-2,3,4a,5,6,11b-hexahydrophen anthro[2,3-*d*][1,3]dioxol-4(1*H*)-one ((±)-2e)

cis-9-Decalinol (±)-**2e** was obtained using the same procedure as for the synthesis of (±)-**2** with keto-epoxide **6e** (22 mg, 0.082 mmol). Purification by chromatography on silica gel (eluent: cyclohexane/ethyl acetate 80:20) gave (±)-**2e** as a yellow solid (20 mg, 89%). R_f=0.68 (cyclohexane/EtOAc 70:30); mp 165–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.71 (s, 1H), 6.57 (s, 1H), 5.87 (dd, J_1=1.2 Hz, J_2=9.6 Hz, 1H), 4.00 (s, 1H), 3.10 (m, 1H), 2.65 (dt, J_1=6.4 Hz, J_2=12.8 Hz, 1H), 2.61 (m, 2H), 2.42 (m, 1H), 1.79 (m, 5H), 1.21 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=214.8, 146.4, 145.8, 136.9, 127.3, 108.5, 106.2, 100.8, 79.9, 45.8, 41.1, 36.8, 30.0, 25.9, 22.4, 20.9 ppm; IR (neat): ν=3481, 2949, 1706, 1504, 1489, 1376, 1240, 1218, 1041, 966, 932, 846 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{16}H_{18}O_4$ $[M+K]^+$, 313.0837; found, 313.0837.

4.10. *cis*-3-(2-Furyl)-10a-hydroxy-4a,7-dimethyl-3,4,4a,9,10,10a-hexahydrophenanthren-1(2*H*)-one ((±)-2g)

cis-9-Decalinol (±)-**2g** was obtained using the same procedure as for the synthesis of (±)-**2** with keto-epoxide **6g** (112 mg, 0.361 mmol). Purification by chromatography on silica gel (eluent: cyclohexane/ethyl acetate 90:10) gave (±)-**2g** as an orange oil (86 mg, 77%). R_f=0.62 (cyclohexane/EtOAc 90:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.31 (m, 1H), 7.16 (d, J=8.0 Hz, 1H), 6.99 (d, J=8.0 Hz, 1H), 6.96 (s, 1H), 6.28 (q, J=1.6 Hz, 1H), 6.02 (d, J=3.6 Hz, 1H), 3.98 (s, 1H), 3.34 (m, 1H), 3.20 (m, 1H), 2.76 (m, 3H), 2.59 (m,

1H), 2.45 (m, 1H), 2.30 (s, 3H), 2.13 (m, 1H), 1.67 (dd, J=1.6, 19.2 Hz, 1H), 1.35 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=213.2, 156.4, 141.6, 140.2, 135.7, 133.7, 129.6, 127.4, 126.2, 110.2, 104.3, 79.7, 46.0, 44.2, 41.4, 33.9, 30.0, 27.0, 25.5, 21.0, 20.9 ppm; IR (neat): ν=3477, 2935, 1707, 1504, 1454, 1383, 1352, 1224, 1191, 1153, 1067, 1047, 1012, 967, 911, 845, 731 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{20}H_{22}O_3$ $[M+H]^+$, 311.1646; found, 311.1642.

4.11. *cis*-5a-Hydroxy-9a-methyl-5,5a,7,8,9,9a-hexahydronaph to[1,2-*b*]thiophen-6-(4*H*)-one ((±)-2h)

cis-9-Decalinol (±)-**2h** was obtained using the same procedure as for the synthesis of (±)-**2** with keto-epoxide **6h** (45 mg, 0.188 mmol). Purification by chromatography on silica gel (eluent: cyclohexane/ethyl acetate 80:20) gave (±)-**2h** as a yellow solid (38 mg, 86%). R_f=0.30 (cyclohexane/EtOAc 80:20); mp 96–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.10 (d, J=5.2 Hz, 1H), 6.75 (d, J=5.2 Hz, 1H), 4.04 (s, 1H), 2.89 (m, 1H), 2.73 (m, 1H), 2.62 (dd, J=7.2, 14.0 Hz, 1H), 2.51 (m, 1H), 2.38 (dd, J=6.4, 12.0 Hz, 1H), 2.12 (dd, J=4.0, 13.6 Hz, 1H), 1.89 (m, 3H), 1.66 (dd, J=6.0, 12.0 Hz, 1H), 1.28 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=214.1, 144.6, 132.8, 127.2, 122.3, 80.2, 46.1, 41.6, 36.9, 30.5, 22.5, 22.3, 21.7 ppm; IR (neat): ν=3468, 2967, 2923, 1704, 1447, 1428, 1377, 1310, 1249, 1174, 1150, 1117, 1080, 1056, 965, 952, 917, 719, 699, 683 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{13}H_{16}O_2S$ $[M+H]^+$, 237.0951; found, 237.0948.

4.12. *cis*-8a-Hydroxy-4a-methyl-3,4,4a,5,8,8a-hexahydronaphtalen-1(2*H*)-one ((±)-2i) and 2-but-3-en-1-yl-3-chloro-2-hydroxy-3-methylcyclohexanone ((±)-14)

cis-9-Decalinol (±)-**2i** and (±)-**14** were obtained using the same procedure as for the synthesis of (±)-**2** with keto-epoxide **6i** (77 mg, 0.426 mmol). Purification by chromatography on silica gel (eluent: cyclohexane/ethyl acetate 95:5) gave (±)-**2i** as a colourless oil (39 mg, 52%) and (±)-**14** as a colourless oil (19 mg, 20%) in a *syn*/*anti* ratio of 90:10. Analysis of (±)-**2i** were identical to the ones reported in the literature.[19a] Analysis of (±)-**14**: R_f=0.65 (cyclohexane/EtOAc 90:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.73 (m, 1H), 4.99 (qd, J_1=1.6 Hz, J_2=17.2 Hz, 1H), 4.95 (qd, J_1=1.6 Hz, J_2=10.0 Hz, 1H), 4.01 (s, 1H), 2.48 (m, 3H), 2.28 (m, 1H), 1.97 (m, 4H), 1.52 (m, 2H), 1.47 (s, 2.7H, Me_{syn}), 1.45 (s, 0.3H, Me_{anti}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=211.1, 137.5, 115.4, 84.9 (*syn*), 76.7 (*anti*), 70.86, 40.2 (*anti*), 39.3 (*syn*), 36.7 (*syn*), 35.1 (*syn*), 34.0 (*anti*), 28.7 (*anti*), 27.2 (*syn*), 26.3 (*anti*), 25.1 (*syn*), 23.7 (*anti*), 21.6 (*syn*), 20.0 (*anti*) ppm; IR (neat): ν=3474, 2968, 1715, 1441, 1381, 1311, 1143, 1112, 1078, 914, 855, 606 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{11}H_{17}ClO_2$ $[M+H]^+$, 217.0995; found, 217.0994.

4.13. *cis*-8a-Chloro-10a-hydroxy-4a-methyldodecahydrophena nthren-1(2*H*)-one ((±)-2j)

cis-9-Decalinol (±)-**2j** was obtained using the same procedure as for the synthesis of (±)-**2** with keto-epoxide **6j** (51 mg, 0.128 mmol). Purification by chromatography on silica gel (eluent: cyclohexane/ethyl acetate 90:10) gave (±)-**2j** as a colourless oil (23 mg, 66%). R_f=0.50 (cyclohexane/EtOAc 80:20); ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.63 (m, 1H), 2.15 (dd, J=6.4, 17.6 Hz, 1H), 2.04 (m, 1H), 1.90 (m, 2H), 1.62 (m, 8H), 1.14 (m, 6H), 0.8 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=212.1, 99.7, 80.6, 57.0, 53.7, 42.8, 39.9, 33.9, 31.3, 25.9, 24.6, 23.4, 23.2, 22.3, 20.2 ppm; IR (neat): ν=3475, 2934, 2861, 1721, 1448, 1093, 1064, 1050, 970, 944, 915, 745 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{15}H_{23}ClO_2$ $[M+Na]^+$, 293.1284; found, 293.1286.

4.14. 6-Chloro-8a-hydroxy-4a-methyl-3,4,4a,7,8,8a-hexahydro naphtalen-1(2*H*)-one ((±)-2k)

cis-9-Decalinol (±)-**2k** was obtained using the same procedure as for the synthesis of (±)-**2** with keto-epoxide **6k** (40 mg, 0.224 mmol). Purification by chromatography on silica gel (eluent: cyclohexane/ethyl acetate 90:10) gave (±)-**2k** as a white solid (41 mg, 89%). Experimental data for (±)-**2k** were identical to the data reported in the literature.[19c]

4.15. 2-[2-(3-Bromophenyl)ethyl]-3-chloro-2-hydroxy-3-methylcyclohexanone ((±)-13)

Compound (±)-**13** was obtained using the same procedure as for the synthesis of (±)-**2** with keto-epoxide **6f** (131 mg, 0.422 mmol). Purification by chromatography on silica gel (eluent: cyclohexane/ethyl acetate 80:20) gave (±)-**13** as a white solid in a *syn*/*anti* ratio of 63:37 (106 mg, 88%). R_f=0.75 (cyclohexane/EtOAc 80:20); mp 62–64 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.30 (m, 2H), 7.13 (t, J=7.6 Hz, 1H), 7.07 (m, 1H), 2.39 (m, 5H), 2.16 (m, 2H), 1.96 (m, 3H), 1.48 (s, 2H, Me_{syn}), 1.42 (s, 1.2H, Me_{anti}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=214.3 (*anti*), 211.1 (*syn*), 143.6 (*syn*), 140.8 (*anti*), 131.7 (*anti*), 131.5 (*syn*), 130.2 (*syn*), 129.6 (*anti*), 129.5 (*anti*), 129.4 (*syn*), 128.1 (*anti*), 127.2 (*syn*), 122.6 (*syn*), 119.7 (*anti*), 91.7 (*anti*), 84.9 (*syn*), 79.7 (*anti*), 76.6 (*syn*), 40.9 (*anti*), 39.3 (*syn*), 37.7 (*syn*), 36.7 (*anti*), 36.6 (*syn*), 36.1 (*anti*), 30.6 (*syn*), 29.0 (*syn*), 25.2 (*syn*), 22.4 (*anti*), 21.6 (*syn*), 20.5 (*anti*) ppm; IR (neat): ν=3471, 2967, 1709, 1593, 1567, 1474, 1426, 1380, 1311, 1154, 1120, 1072, 978, 847, 783, 732, 688, 669, 601 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{15}H_{18}BrClO_2$ $[M+NH_4]^+$, 361.0444; found, 361.0446.

4.16. 3-Chloro-2-hydroxy-3-methyl-2-[3-(3,4,5-trimethoxyphenyl)propyl]cyclohexanone ((±)-16)

Compound (±)-**16** was obtained using the same procedure as for the synthesis of (±)-**2** with keto-epoxide **6m** (58 mg, 0.174 mmol). Purification by chromatography on silica gel (eluent: cyclohexane/ethyl acetate 80:20) gave (±)-**16** as a colourless oil in a *syn*/*anti* ratio of 90:10 (48 mg, 74%). R_f=0.38 (cyclohexane/EtOAc 60:40); ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.34 (s, 2H), 4.01 (s, 1H), 3.83 (s, 6H), 3.80 (s, 3H), 2.13 (m, 8H), 1.91 (m, 2H), 1.62 (m, 2H), 1.45 (s, 2.6H, Me_{syn}), 1.30 (s, 0.3H, Me_{anti}) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=212.5 (*anti*), 211.1 (*syn*), 153.2, 137.5 (*syn*), 136.3 (*anti*), 105.3, 85.1 (*syn*), 78.8 (*anti*), 76.8 (*syn*), 60.9 (*syn*), 56.2 (*syn*), 39.3 (*syn*), 38.6 (*anti*), 37.5 (*anti*), 36.5 (*syn*), 36.3 (*syn*), 36.2 (*anti*), 35.2 (*syn*), 33.9 (*anti*), 26.3 (*anti*), 25.1 (*syn*), 24.7 (*syn*), 21.5 (*syn*), 19.4 (*anti*), 17.4 (*anti*) ppm; IR (neat): ν=3479, 2938, 2838, 1713, 1589, 1508, 1456, 1420, 1341, 1239, 1182, 1126, 1009 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{19}H_{27}ClO_5$ $[M+H]^+$, 371.1625; found, 371.1629.

4.17. 2-Hydroxy-3-methyl-2-(3-methylbenzyl)cyclohex-3-en-1-one (15)

Compound **15** was obtained using the same procedure as for the synthesis of (±)-**2** with keto-epoxide **6l** (93 mg, 0.403 mmol). Purification by chromatography on silica gel (eluent: cyclohexane/ethyl acetate 95:5) gave **15** as a yellow solid (69 mg, 74%). R_f=0.27 (cyclohexane/EtOAc 95:5); mp 49–52 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.14 (t, J=7.6 Hz, 1H), 7.03 (d, J=7.6 Hz, 1H), 6.97 (s, 1H), 6.92 (d, J=7.6 Hz, 1H), 6.72 (m, 1H), 3.71 (s, 1H), 2.79 (m, 2H), 2.54 (m, 1H), 2.45 (m, 1H), 2.32 (s, 3H), 2.11 (m, 1H), 1.97 (m, 1H), 1.85 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=202.4, 145.1, 137.8, 135.6, 133.6, 131.2, 128.0, 127.6, 127.3, 75.8, 42.7, 33.9, 24.3, 21.5, 15.9 ppm; IR (neat): ν=3486, 2922, 1668, 1449, 1431, 1362, 1345, 1218, 1107, 1057, 1022, 882, 792, 770, 721, 712 cm^{-1}; HRMS (ESI, m/z): calcd for $C_{15}H_{18}O_2$ $[M+H]^+$, 231.1385; found, 231.1381.

4.18. (1*S*)-2-[2-(3-Isopropyl-2-methoxyphenyl)ethyl]-3-methyl cyclohex-2-en-1-ol ((*S*)-17)

$BH_3 \cdot Me_2S$ (110 μL, 1.117 mmol, 1.6 equiv) was added dropwise at 0 °C to a stirred suspension of (*R*)-oxazaborolidine (232 mg,

0.838 mmol, 1.2 equiv) in dry tetrahydrofuran (9 mL). After 30 min at 0 °C, a solution of α,β-unsaturated ketone **8** (200 mg, 0.698 mmol, 1.0 equiv) in dry tetrahydrofuran (11 mL) was added dropwise and the mixture was stirred for 1 h at 0 °C. Methanol was then slowly added and the mixture concentrated. The residue was purified by chromatography on silica gel (eluent: cyclohexane/ethyl acetate 70:30) to give (*S*)-**17** as a colourless oil (196 mg, 97%) with an enantiomeric excess of 92%. R_f=0.54 (cyclohexane/EtOAc 70:30); $[\alpha]_D$ +32.2 (*c* 1 M, MeOH) ; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.02 (m, 3H), 4.10 (br, 1H), 3.74 (s, 3H), 3.28 (quint, *J*=6.6 Hz, 1H), 2.43 (m, 2H), 1.57–1.93 (m, 9H), 1.47 (s, 3H), 1.23 (d, *J*=6.6 Hz, 3H), 1.19 (d, *J*=6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.7, 141.8, 135.2, 132.8, 131.3, 128.0, 124.6, 124.5, 61.8, 38.9, 32.4, 32.3, 32.1, 29.9, 26.5, 24.2, 23.9, 19.0, 17.9 ppm; IR (neat): ν=3422, 2958, 2934, 1465, 1460, 1257, 1203, 1167, 1052, 1015, 765, 680, 669 cm^{-1}; HRMS (ESI, *m*/*z*): calcd for $C_{19}H_{28}O_2$ $[M+H]^+$, 289.2168; found, 289.2164.

4.19. (1*S*,2*S*,6*R*)-1-[2-(3-Isopropyl-2-methoxyphenyl)ethyl]-6-methyl-7-oxabicylo[4.1.0]heptan-2-ol ((1*S*,2*S*,6*R*)-18)

$NaHCO_3$ (103 mg, 1.22 mmol, 2.0 equiv) and *m*-CPBA (180 mg, 0.730 mmol, 1.2 equiv) were added at 0 °C to a solution of (*S*)-**17** (175 mg, 0.608 mmol, 1.0 equiv) in dichloromethane (6.5 mL). After 1 h at 0 °C, an aqueous solution of sodium thiosulfate 1 M (6.5 mL) was added and the mixture was partionned between diethyl ether (16.5 mL) and $NaHCO_3$ saturated. The organic phase was washed with $NaHCO_3$ saturated (6 mL) and brine (2×6 mL), dried over sodium sulfate and evaporated to give (1*S*,2*S*,6*R*)-**18** as a colourless solid (185 mg, quantitative) with an enantiomeric excess of 93%. R_f=0.40 (cyclohexane/EtOAc 80:20); $[\alpha]_D$ +29.4 (*c* 1 M, MeOH) ; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.11 (dd, J_1=7.2 Hz, J_2=3.0 Hz, 1H), 7.02 (m, 2H), 4.05 (br s, 1H), 3.75 (s, 3H), 3.28 (sept., *J*=6.8 Hz, 1H), 2.74 (t, *J*=8.6 Hz, 2H), 2.25 (m, 2H), 1.41–1.84 (m, 8H), 1.21 (d, *J*=7.0 Hz, 6H), 1.15 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.7, 142.1, 134.4, 127.7, 125.0, 124.5, 67.3, 66.9, 66.3, 61.8, 33.1, 31.3, 31.1, 27.0, 26.4, 26.2, 24.2, 20.1, 15.7 ppm; IR (neat): ν=3326, 2935, 1968, 1461, 1428, 1251, 1203, 1167, 1080, 1049, 1012, 862, 796, 765 cm^{-1}; HRMS (ESI, *m*/*z*): calcd for $C_{19}H_{28}O_3$ $[M+H]^+$, 305.2117; found, 305.2115.

4.20. (1*S*)-2-[2-(3-Isopropyl-2-methoxyphenyl)ethyl]-3-methylcyclohex-2-en1-ol ((1*R*,6*R*)-19)

A solution of (1*S*,2*S*,6*R*)-**18** (187 mg, 0.648 mmol, 1.0 equiv) in dry dichloromethane (1.2 mL) was added at room temperature to a solution of Dess–Martin periodinane (314 mg, 0.617 mmol, 1.0 equiv) in dry dichloromethane (400 μL) and the mixture was stirred for 2 h. After concentration, the residue was purified by chromatography on silica gel (eluent: cyclohexane/ethyl acetate 80:20) to give (1*R*,6*R*)-**19** as a white solid (151 mg, 86%). The recorded experimental data (^{1}H, ^{13}C, IR and MS) were identical to those found for **6a**. $[\alpha]_D^{24}$ +30.2 (*c* 1 M, MeOH) .

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Supplementary data

Procedures for the preparation of unknown starting C2-substituted 3-methylcyclohexenones, ^{1}H and ^{13}C NMR spectra as well as HPLC chromatograms for enantioselectivity exploration are given. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.08.050. These data include MOL files and InChIKeys of the most important compounds described in this article.

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