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A new approach to 2,2-disubstituted chromenes and tetrahydroquinolines through intramolecular cyclization of chiral 3,4-epoxy alcohols

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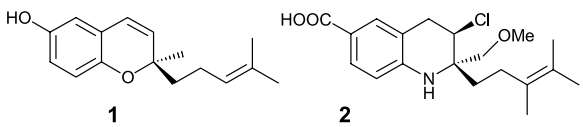
Abstract—An efficient route to chiral chromene and tetrahydroquinoline ring models **3** and **4** was developed by means of the vanadium epoxidation of chiral homoallylic alcohols **12** and **19** followed by an intramolecular epoxide opening of 3,4-epoxy alcohols **14** and **20**. The configuration of all compounds was confirmed using NMR analysis.

1. Introduction

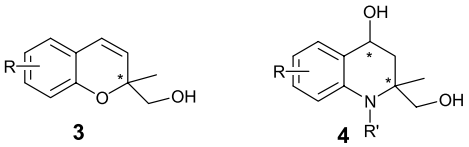
O and *N*-Heterocyclic compounds have attracted considerable attention because of their functionality in pharmaceutical chemistry. In particular, synthesis of benzo-fused *O* and *N*-heterocyclic compounds such as chromenes[1] and tetrahydroquinolines[2] is very important because they are found in a variety of natural products, which exert a broad range of bioactivities (e.g., antioxydants,[3] enzyme inhibitors,[4] antitumor agents,[5] antibiotic agents[6]). Numerous publications[7] described the preparation of these important classes of heterocycles. However, it remains a great challenge to establish stereogenic quaternary carbon on both chromene and tetrahydroquinoline ring systems. Only a few publications[8] have described an access to these types of compounds and have been directed to specific molecules such as, for example, cordiachromene[9] **1** or virantmycin[6f,g] **2** (Fig. 1).



1 2

Figure 1.

In a previous article, we described an efficient three-step procedure for the synthesis of substituted 2-hydroxymethyl-2-methyl-2*H*-chromenes.[10] Herein, we wish to report the extension of our versatile procedure to optically active 2-hydroxymethyl-2-methyl-2*H*-chromenes **3** and to another class of heterocycles, 2-hydroxymethyl-2-methyl-1,2,3,4-tetrahydroquinolin-4-ols **4** (Fig. 2).



3 4

Figure 2.

2. Results and discussion

2.1. Retrosynthetic analysis

A retrosynthetic analysis of target molecule **3** is delineated in Scheme 1. The formation of 2*H*-chromene moiety can be achieved by a ring closure of key chiral epoxide **6** under acidic conditions. This ring closure through path a (6-*exo-tet*) is a more favored process than path b (7-*endo-tet*) following Baldwin's rules.[11] Key intermediate **6** is based on a 3,4-epoxy-3-methyl-1-(2-subtituted phenyl)butan-1-ol subunit. The desired oxirane function can be introduced by a stereoselective epoxidation of protected homoallylic alcohol **7** with vanadium (IV)/*tert*-butylhydroperoxide as oxidants. Required homoallylic alcohol **7** can be synthesized by asymmetric allylation of either various substituted 2-hydroxybenzaldehyde **8** with (+) or (−)-β-methallyldiisopinocampheylborane **9**. Homoallylic alcohols can also be obtained by asymmetric reduction of ketone **10**

Keywords: Chromene; Tetrahydroquinoline; 2*H*-1-Benzopyrane.
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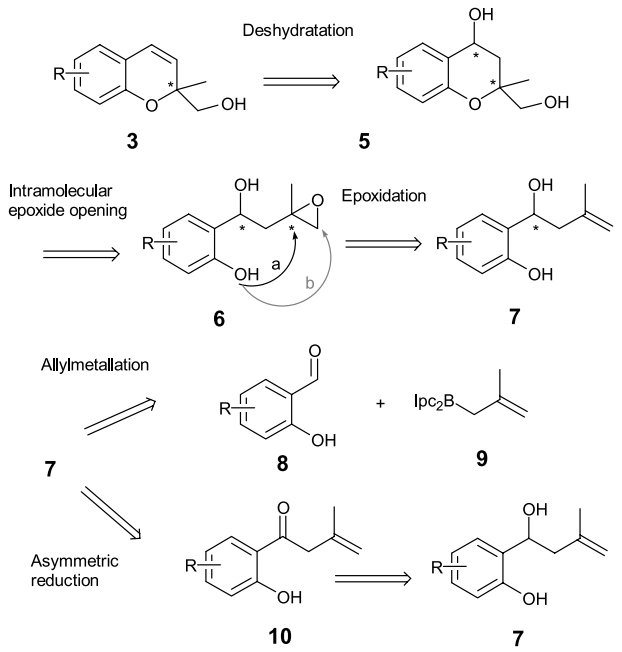
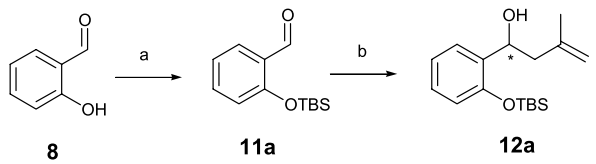
using CBS-oxazaborolidine. This strategy will be applied to nitrogen analogues to form target tetrahydroquinoline **4**.



Scheme 1. Retrosynthetic analysis of 2,2-disubstituted chromenes **3**.

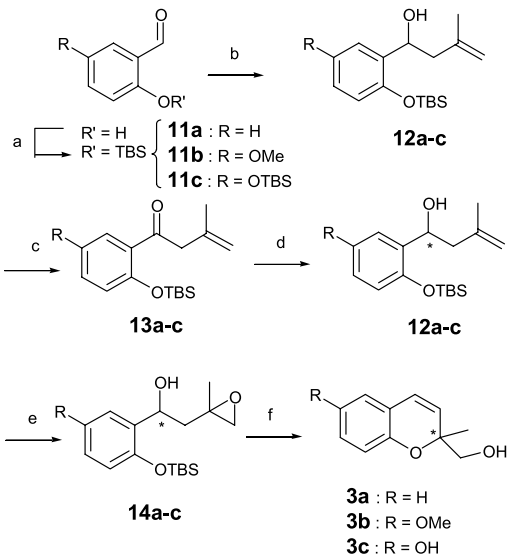
2.2. Asymmetric synthesis of 2,2-disubstituted chromenes 3

As depicted in Scheme 2, the reaction of salicylaldehyde with *tert*-butyldimethylsilylchloride (TBDMS-Cl) and imidazole in DMF afforded the corresponding 2-OTBS benzaldehyde **11a** in excellent yield. Brown's asymmetric allylation[12] (method A) of compounds **11a** with β-methallyldiisopinocampheylborane **9**, prepared from (+) or (−)-β-chlorodiisopinocampheylborane ((+) or (−)-Ipc_2BCl) and 2-methylpropenylmagnesium chloride, afforded corresponding chiral homoallylic alcohols (+) or (−)-**12a** in good yields and 80% ee (best value, Table 1).



Scheme 2. Reagents and conditions: (a) TBDMSCl, imidazole, DMF, rt; (b) (+) or (−)-methallyldiisopinocampheylborane **9**, THF, −78 °C, 2 h.

Accordingly, an improvement in ee values was necessary, so we turned our attention to a synthesis of enantiopure compounds **12a-c**, based on asymmetric reduction of corresponding ketones **13a-c** using (*R*) or (*S*)-CBS-oxazaborolidines[13] as chiral reducing agents (method B in Table 1, Scheme 3). β,γ-Unsaturated ketones **13a-c** were obtained by treatment of compounds **11a-c** with an excess of 2-methylpropenylmagnesium chloride followed by oxidation with Dess–Martin periodinane (DMP). Enantioselective reduction of β,γ-unsaturated ketones **13a-c** with (*R*) or (*S*)-CBS-oxazaborolidine reagent and catecholborane at −60 °C led to homoallylic alcohols **12a-c** with quantitative yields and ee values ranging from 85 to 95% (Table 1).



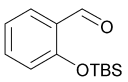
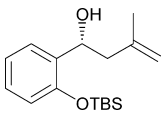
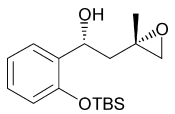
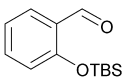
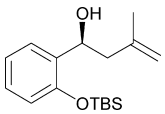
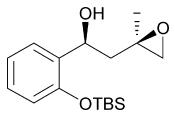
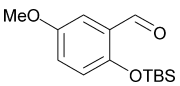
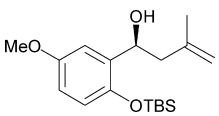
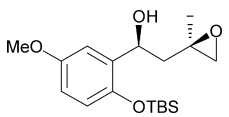
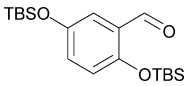
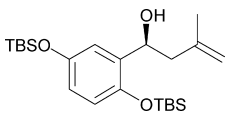
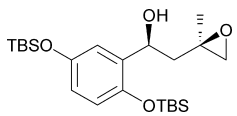
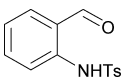
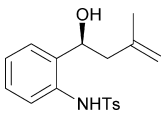
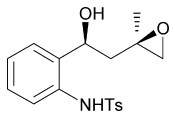
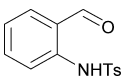
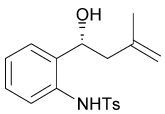
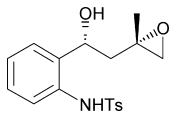
Scheme 3. Reagents and conditions: (a) TBDMSCl, imidazole, DMF, rt; (b) 2-methylpropenylmagnesium chloride, THF, 50 °C, 3 h; (c) DMP, DCM, 0 °C, 1 h; (d) (*R*) or (*S*)-CBS oxazaborolidine, catecholborane, toluene, −60 °C; (e) TBHP, $VO(acac)_2$, DCM, −10 °C, 5 h; (f) (i) TBAF, THF, 0 °C; (ii) CSA (4 mol%), toluene, reflux, 16 h.

The next step was the stereoselective epoxidation of chiral homoallylic alcohols **12a-c** by the usual and cheap procedure using *tert*-butylhydroperoxide (TBHP) and a catalytic amount of vanadylacetylacetonate ($VO(acac)_2$).[14] In each case, epoxyalcohols **14a-c** were obtained in both good yields and diastereoselectivities (Table 1, Scheme 3). Subsequent *O*-silyldeprotection of **14a-c** with TBAF followed by the ring closure in refluxing toluene with a catalytic amount of camphor sulfonic acid (CSA) (4 mol%) gave directly chromenes **3a-c**, as reported in a recent paper.[10] It should be noted that the overall process permitted synthesis of chromenes with good yields, but in all cases with a loss of optical purity (based on the ee value of starting epoxyalcohols **14a-c** (Table 2, entries 1–4). This result could be interpreted by a lack of selectivity during the cyclization step under acidic conditions or by a possible racemization via a retro-Claisen rearrangement, which has already been observed on such compounds upon exposure to light irradiation.[15]

In order to rationalize this result, we have first studied nucleophile centres which should be involved into the intramolecular cyclization reaction. According to Baldwin's rules, two pathways are favored. Scheme 4 presents the structures of the possible intermediates corresponding to this intramolecular cyclization reaction. For 6-*exo-tet* and 4-*exo-tet* favored cyclization reactions, which, respectively, involve one or two Walden inversion, two stereoisomers related to (+) or (−)-**3a** can be formed. These two competitive ring closures could explain the observed loss of optical purity for chromenes **3**.

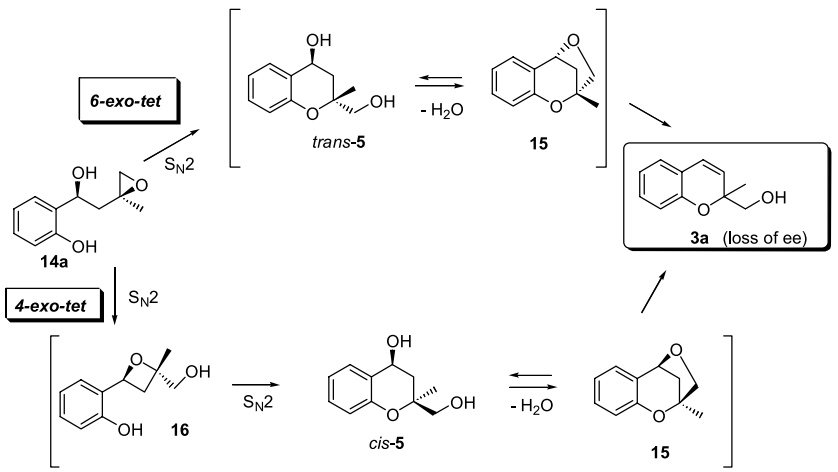
Alternatively, the hypothesis of a racemization reaction has

Table 1. Allylation and epoxidation reactions

Entry	Aldehydes	Method	Alcohols	Yields (%)[a] (ee)[b]	Epoxides	Yields (%)[a] (de)[c]
1		A[d]		79 (80%)		72 (84%)[e]
	11a	B[f]	(+)-(*R*)-**12a**	75 (93%)	(+)-(1*R*,3*S*)-**14a**	
2		A[g]		74 (80%)		72 (86%)[e]
	11a	B[h]	(−)-(*S*)-**12a**	72 (95%)	(−)-(1*S*,3*R*)-**14a**	
3		B[h]		70 (90%)		73 (84%)[e]
	11b		(−)-(*S*)-**12b**		(−)-(1*S*,3*R*)-**14b**	
4		B[h]		75 (85%)		70 (82%)[e]
	11c		(−)-(*S*)-**12c**		(−)-(1*S*,3*R*)-**14c**	
5		A[g]		84 (82%)		89 (82%)
	18		(+)-(*S*)-**19**		(+)-(1*S*,3*R*)-**20**	
6		A[d]		80 (84%)		96 (84%)
	18		(−)-(*R*)-**19**		(−)-(1*R*,3*S*)-**20**	

[a] Isolated yields.
[b] Enantiomeric excess were determined by HPLC.
[c] Diastereomeric excess determined by ^{1}H NMR spectroscopy.
[d] Reaction carried out with methallyldiisopinocampheylborane **9** prepared from (+)-DIPCl.
[e] Diastereomeric excess of epoxidation reaction with compounds **12** prepared by method B.
[f] Reaction carried out with (*S*)-CBS oxazaborolidine.
[g] Reaction carried out with methallyldiisopinocampheylborane **9** prepared from (−)-DIPCl.
[h] Reaction carried out with (*R*)-CBS oxazaborolidine.

also been taken in account. Exposure of chiral chromene **17**[9b] to the same experimental conditions used for the cyclization of **14** (refluxed toluene, CSA 4 mol%) led to a decrease in the optical activity of **17** (Scheme 5). Half-life for racemization of **17** is around 96 h. This result gave an important information about the rate of racemization of 2,2-dialkylchromene via a thermally induced retro-Claisen rearrangement.

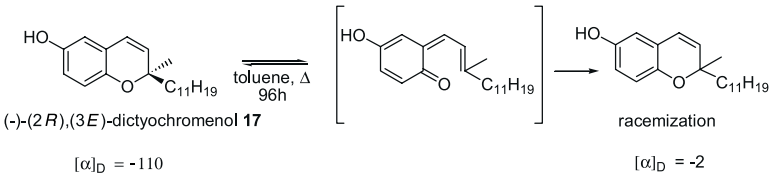


Scheme 4. Hypothetical mechanism for the formation of chromenes **3**.

From all these results, it seems that both the thermally induced racemization and the two possible ring closure pathways might limit stereoselectivity of this intramolecular cyclization reaction accounting for poor optical purity of chromenes **3**.

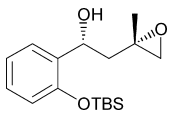
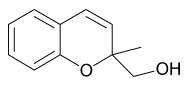
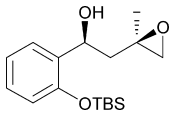
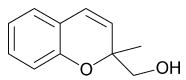
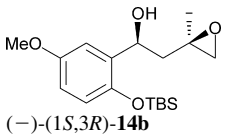
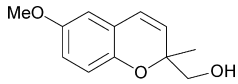
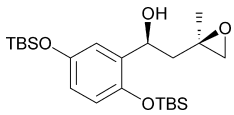
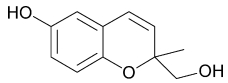
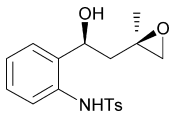
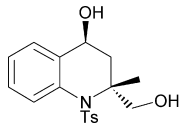
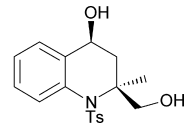
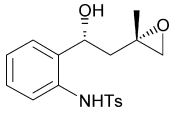
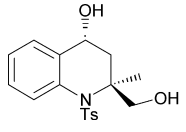
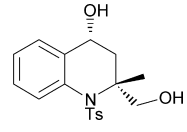
2.3. Asymmetric synthesis of 2,2-disubstituted-1,2,3,4-tetrahydroquinolin-4-ols 4

Tos-protected aminobenzaldehyde **18** was readily available in high yield by a two-step sequence on multigram scale from commercially available 2-aminobenzyl alcohol. After oxidation with manganese dioxide in dichloromethane to the corresponding aldehyde,[16] the amino group was protected as a sulfonamide. Compound **18** was easily transformed to homoallylic alcohols **19** (80<ee<86%) which were then converted to corresponding epoxyalcohols **20** using the same experimental conditions as above for the preparation of **14a-c** (Scheme 6, Table 1). It is noteworthy that in order to increase the ee of compounds **19**, we attempted, without any success, asymmetric reduction of the corresponding ketone.[17] At this stage in our synthetic strategy, behavior of **20** in the intramolecular epoxide opening sequence was investigated using conditions described by Morimoto et al.[6f,g] Treatment of **20** with trifluoroacetic acid in toluene at room temperature for 16 h expectedly provided desired 1,2,3,4-tetrahydroquinolin-4-ol **4** as the exclusive product of cyclization reaction. Moreover,

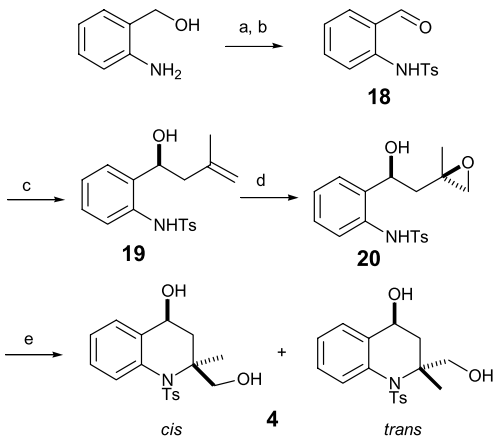


Scheme 5. Racemization of **17**.

Table 2. Synthesis of chromene **3a-c** and tetrahydroquinoline **4**

Entry	Epoxides	Alcohols		Yields (%)[a] (ee)
1	 (+)-(1*R*,3*S*)-**14a**	 (+)-**3a**		80 (46%)[b]
2	 (−)-(1*S*,3*R*)-**14a**	 (−)-**3a**		80 (44%)[b]
3	 (−)-(1*S*,3*R*)-**14b**	 (−)-**3b**		75 (43%)[b]
4	 (−)-(1*S*,3*R*)-**14c**	 (−)-**3c**		68 (35%)[b]
5	 (+)-(1*S*,3*R*)-**20**	 (+)-*trans*-(2*R*,4*S*)-**4**	 (+)-*cis*-(2*S*,4*S*)-**4**	45 (+)-*trans*-**4**: (88%)[c] (+)-*cis*-**4**: (40%)[c]
6	 (−)-(1*R*,3*S*)-**20**	 (−)-*trans*-(2*S*,4*R*)-**4**	 (−)-*cis*-(2*R*,4*R*)-**4**	58 (−)-*trans*-**4**: (94%)[c] (−)-*cis*-**4**: (63%)[c]

[a] Isolated overall yields.
[b] Enantiomeric excesses determined by HPLC on a chiral column.
[c] Enantiomeric excesses determined by HPLC on a chiral column after isolation of each diastereomer by flash chromatography.



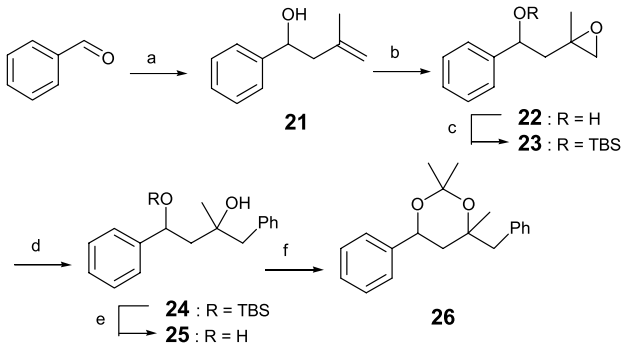
Scheme 6. Reagents and conditions: (a) MnO_2, DCM, rt; (b) acid *p*-toluene sulfonyl chloride, DCM, pyridine, rt; (c) (+) or (−)-methallyldiisopinocampheylborane **9**, THF, −78 °C, 2 h; (d) TBHP, $VO(acac)_2$, DCM, −5 °C, 5 h; (e) 2 equiv. of TFA, toluene, rt, 16 h.

it should be pointed out that compound **4** was obtained as a mixture of diastereomers (50:50) which were easily separated by column chromatography to furnish diastereomerically pure tetrahydroquinolines (+)-*cis*-**4** and (+)-*trans*-**4** from (+)-**20** and (−)-*cis*-**4** and (−)-*trans*-**4** from (−)-**20** in good overall yields (Table 2, entries 5 and 6). As for chromene's series, the loss of stereoselectivity in the last step might be explained by assuming that the two favored mechanisms are competitive.

In addition, the enantiomeric excess in which these heterocycles **4** were obtained, was determined by chiral HPLC showing that little or no racemization occurred at C1 during the process from **20** to tetrahydroquinoline **4** (Table 2).

2.4. Determination of relative and absolute configuration of the products

2.4.1. Determination of absolute configuration of 3,4-epoxy alcohols 14. While the oxidative reaction of homoallylic alcohols using vanadium (IV)[14] as a catalyst often gave epoxy alcohols with both good yields and diastereoselectivities, our major intention was to establish the relative configuration between C1 and new C3 stereogenic centre created during epoxidation and consequently, the absolute configuration at C3. With this idea in mind, we envisaged the conversion of epoxy alcohols to their corresponding six-membered acetonides in order to study their conformational properties by NMR spectroscopy. In order to simplify this study, the synthetic sequence described in Scheme 7 was carried out with epoxy alcohol **22** instead of more complex epoxy alcohols **14**. Thus, epoxy alcohol **22** was prepared in two steps starting from benzaldehyde and 2-methylpropenylmagnesium chloride followed by oxidation of the resultant product with *tert*-butylhydroperoxide (TBHP) and a catalytic amount of vanadylacetylacetonate ($VO(acac)_2$). According to these experimental conditions, **22** was obtained in good yield as a 80:20 mixture of diastereomers. Then, **22** was converted to acetonide **26** in a four-step sequence involving protection of the secondary alcohol, regioselective addition of phenyllithium, *O*-silyl deprotection and acetalization.



Scheme 7. Reagents and conditions: (a) 2-methylpropenylmagnesium chloride, THF, 50 °C, 3 h; (b) TBHP, $VO(acac)_2$, DCM, 0 °C, 8 h; (c) TBDMSCl, imidazole, DMF, rt; (d) PhLi, $BF_3{\cdot}Et_2O$, THF, −78 °C; (e) TBAF, THF, rt; (f) CSA, DMP, rt.

The relative configuration of **26** was determined by ^{13}C NMR analysis as shown in Figure 3.

The chemical shifts of the methyl of the acetal for major compound **26** were in accord with a 1,3-*syn* stereochemistry.[18] These results confirmed the *syn* stereoselectivity of the epoxidation with vanadium (IV)[14] as a catalyst.

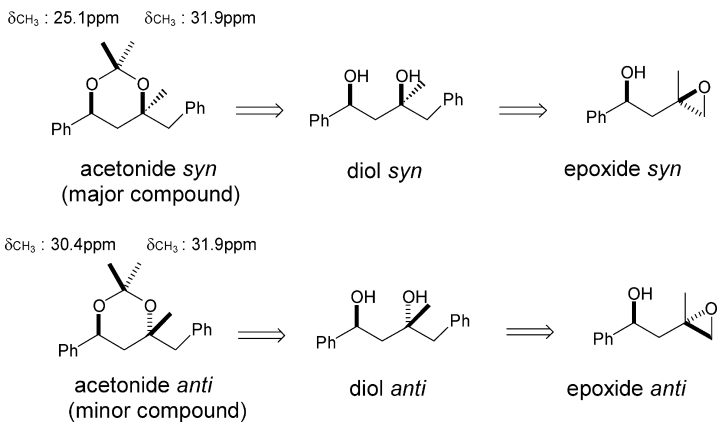


Figure 3. ^{13}C NMR analysis of epoxides.

2.4.2. Determination of absolute configuration of tetrahydroquinolines 4. The configurational assignment of compounds **4** was effected by NOESY experiments. As summarized in Figure 4, NOESY spectra clearly showed a significant NOE corresponding to the dipolar interactions between H4 and H2′ for compounds (−)-*trans*-**4** and (+)-*trans*-**4** when either H4 or H2′ were irradiated. This suggests a *cis* configuration between them for *trans*-**4**. On the other hand, the absence of a NOE enhancement on H4 for *cis*-**4** when H2′ was irradiated suggests a *trans* configuration of the latters. This result was confirmed by a NOE enhancement of H4 by irradiation of CH_3 even if it is difficult to evaluate because of interactions between H4 and H3 in the same time (same chemical shifts for H3 and CH_3). Therefore, the determined *cis* configuration between H4 and H2′ of *trans*-**4** confirms (2*R*,4*S*) and (2*S*,4*R*) absolute configuration of the stereogenic centres of (+)-*trans*-**4** and (−)-*trans*-**4**. The *cis* configuration between H4 and CH_3 of *cis*-**4** allows us to assign (2*S*,4*S*) and (2*R*,4*R*) absolute configuration of stereogenic centres of (+)-*cis*-**4** and (−)-*cis*-**4** compounds.

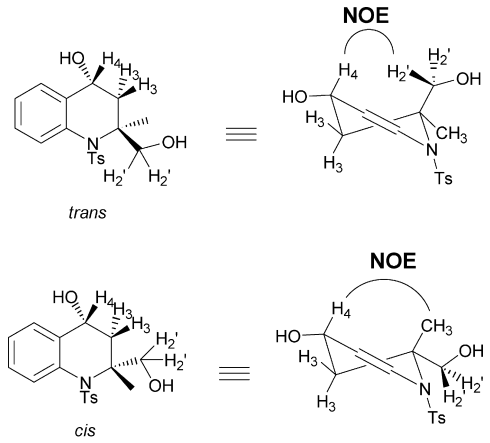


Figure 4. NOE correlation observed in *cis*- and *trans*-**4**.

3. Conclusion

In summary, we successfully extended our method for the stereoselective synthesis of chromene and tetrahydroquinoline rings. If the synthetic utility of the method was limited because of racemization of chromenes, the diastereomeric mixtures of tetrahydroquinolines were easily separated by column chromatography and the absolute configuration of diastereomers was thus assigned.

4. Experimental

4.1. Apparatus

^1H and ^{13}C NMR spectra were recorded on Bruker AC 200 and Bruker AMX 400 spectrometers in $CDCl_3$ as the solvent and TMS as the internal standard; chemical shifts (δ) are expressed in ppm and coupling constants (J) in Hertz. IR spectra were recorded on a Bruker vector 22 spectrometer. Mass spectra (*m*/*e* (% base peak)) were recorded on HP 5889A spectrometer in EI mode (70 eV) or in CI mode (with CH_4 or NH_3 as reacting gas). For high performance liquid chromatography (HPLC) analysis, a Hewlett–Packard model (HP 1050) equipped with a UV detector (254 nm) and a CHIRALCEL OD-H column were employed. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Melting points were determined on a C. REICHERT microscope apparatus and were uncorrected. Elemental analysis were carried out by CNRS Analysis Laboratory, Vernaison, France, on a Perkin–Elmer 2400 C, H, N elemental analyser.

4.2. Chemicals

Every starting material was obtained from commercial suppliers and used without further purification. Dichloromethane, ethylacetate were dried by distillation over P_2O_5. Diethylether, THF, benzene and toluene were distilled from sodium.

4.3. General procedure for formation of silylether 11a-c

To a solution of phenol derivative (3.5 mmol), imidazole (1 g, 14.8 mmol) in DMF (10 mL) was added *tert*-butyldimethylsilyl chloride (810 mg, 5.4 mmol). The reaction was heated 20 h at 80 °C, then 50 mL of water and 50 mL of EtOAc were added. The aqueous layer was extracted with EtOAc (3×40 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (9:1, petroleum ether/EtOAc) to give the silylether **11a-c**.

4.3.1. 2-*tert*-Butyldimethylsilyloxybenzaldehyde 11a. Compound **11a** was obtained from salicyladehyde as a colorless oil (740 mg, 90% yield); ^1H NMR (200 MHz, $CDCl_3$): δ_H 0.26 (s, 6H, $2SiCH_3$), 1.01 (s, 9H, $3CH_3$), 6.85–7.82 (m, 4H, H_{ar}), 10.45 (s, 1H, CHO); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ_C −4.3, −2.9, 18.3, 25.6 (3C), 120.1, 121.4, 127.1, 128.2, 135.6, 158.3, 190.1; IR (film) ν 2956, 2931, 2859, 1689, 1599, 1479, 1254 cm^{-1}; MS-CI *m*/*z* (relative intensity) 237 (M+1, 100), 221 (30), 179 (28).

4.3.2. 4-Methoxy-2-*tert*-butyldimethylsilyloxybenzaldehyde 11b. Compound **11b** was obtained from 2-hydroxy-5-methoxybenzaldehyde (456 mg, 3.0 mmol) as a colorless oil (718 mg, 90% yield); ^1H NMR (200 MHz, $CDCl_3$): δ_H 0.24 (s, 6H, $2SiCH_3$), 1.01 (s, 9H, $3CH_3$), 3.80 (s, 3H, OMe), 6.80–7.28 (m, 3H, H_{ar}), 10.41 (s, 1H, CHO); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ_C −4.4 (2C), 18.3, 25.6 (3C), 55.7, 109.5, 121.6, 123.9, 127.1, 153.4, 154.0, 190.0; IR (film) ν 2956, 2931, 2886, 2858, 1683, 1489 cm^{-1}; MS-EI *m*/*z* (relative intensity) 266 (M^+, 0), 251 (1), 209 (100), 191 (12), 166 (19).

4.3.3. 2,5-Di-*tert*-butyldimethylsilyloxybenzaldehyde 11c. Compound **11c** was obtained from 2,5-dihydroxybenzaldehyde (420 mg, 3.0 mmol) as a colorless oil (660 mg, 90% yield); ^1H NMR (200 MHz, $CDCl_3$): δ_H 0.16 (s, 6H, $2CH_3$), 0.23 (s, 6H, $2CH_3$), 0.96 (s, 9H, $3CH_3$), 1.00 (s, 9H, $3CH_3$), 6.72–7.25 (m, 3H, H_{ar}), 10.37 (s, 1H, CHO); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ_C −4.5 (2C), −4.4 (2C), 18.1, 18.3, 25.6 (6C), 117.6, 121.1, 127.4, 127.9, 149.8, 153.4, 189.9; IR (film) ν 2956, 2931, 2859, 1689, 1488 cm^{-1}; MS-CI *m*/*z* (relative intensity) 367 (M+1, 100), 308 (11).

4.4. Preparation of methallylborane reagents 9

To a solution of diisopinocampheylborane chloride (4 equiv.) in anhydrous diethyl ether (20 mL) at 0 °C under argon was added dropwise a solution of 2-methylpropenyl magnesium chloride (1.5 equiv.) in THF. The reaction mixture was stirred 1 h at 0 °C and 1 h at room temperature. The formation of methallyldiisopinocampheylborane **9** is indicated by precipitation of the magnesium salts. The reagent can be readily isolated as a clear solution, free of magnesium salts, by passing the reaction mixture through a filtration chamber.

4.5. Typical procedure for preparation of homoallylic alcohols 12a

To the precedent clear filtrate **9** (free of magnesium salts) was added, dropwise, at −78 °C and under argon, a solution of compound **11a** (1 equiv.) in anhydrous THF (10 mL). The mixture was stirred for 3 h until TLC showed complete disappearance of starting material. The reaction mixture was then hydrolyzed with 1 N HCl (12 mL) and the organic layer was washed with brine (20 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was heated 1 h in a Kugelrohr at 100 °C under 5 mbar in order to remove most of isopinocampheol formed during the reaction. The residue was purified by column chromatography on silica gel (8:2, petroleum ether/EtOAc).

4.5.1. (+)-(1*R*)-3-Methyl-1-(2-*tert*-butyldimethylsilyloxyphenyl)but-3-en-1-ol 12a. Compound (+)-(*R*)-**12a** was obtained from **11a** and **9** (prepared with (+)-DIP-Cl) as a pale yellow solid in 79% yield; $[\alpha]_D^{20}=+38.8$ ($c=1.2$, acetone); ee=80%; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.27 (s, 3H, $SiCH_3$), 0.28 (s, 3H, $SiCH_3$), 1.02 (s, 9H, $3CH_3$), 1.80 (s, 3H, CH_3), 2.27 (d, 1H, $J=3.2$ Hz, OH), 2.33 (dd, 1H, $J=14$, 9.6 Hz, H^2), 2.52 (dd, 1H, $J=14$, 3.2 Hz, H^2), 4.86 (s, 1H, H^4), 4.92 (s, 1H, H^4), 5.15 (dt, 1H, $J=3.2$, 3.2, 9.6 Hz, H^1), 6.79 (d, 1H, $J=8.0$ Hz, H_{ar}), 6.96 (dd, 1H, $J=7.2$, 7.6 Hz, H_{ar}), 7.13 (ddd, 1H, $J=7.2$, 8.0, 1.6 Hz, H_{ar}), 7.44 (dd, 1H, $J=7.6$, 1.6 Hz, H_{ar}); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ_C −4.1 (2C), 18.2, 22.4, 25.8 (3C), 46.3, 66.3, 113.7, 118.0, 121.2, 126.7, 127.8, 134.2, 142.8, 152.2; IR (film) ν 3424, 2956, 2931, 2859, 1488, 1254 cm^{-1}; MS-EI *m*/*z* (relative intensity) 292 (M^+, 1), 277 (1), 237 (62), 165 (38), 73 (100).

4.5.2. (−)-(1*S*)-3-Methyl-1-(2-*tert*-butyldimethylsilyloxyphenyl)but-3-en-1-ol 12a. Compound (−)-(*S*)-**12a** was obtained from **11a** and **9** (prepared with (−)-DIP-Cl) as a pale yellow solid in 74% yield; $[\alpha]_D^{20}=-35.9$ ($c=1.3$, acetone); ee=80%.

4.6. General procedure for the formation of racemic homoallylic alcohol 12a-c from aldehyde 11a-c

To a solution of 2-methylpropene magnesium chloride (0.6 M in THF) at −30 °C was added dropwise a solution of aldehyde **11a-c** (2.1 mmol) in THF (10 mL). The reaction was stirred 1 h at room temperature and then quenched with a saturated aqueous solution of NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (3×20 mL), the combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (9:1, petroleum ether/EtOAc).

4.6.1. 3-Methyl-1-(2-*tert*-butyldimethylsilyloxyphenyl)but-3-en-1-ol 12a. Compound **12a** was obtained from **11a** as a colorless oil in 98% yield.

4.6.2. 3-Methyl-1-(5-methoxy-2-*tert*-butyldimethylsilyloxyphenyl)but-3-en-1-ol 12b. Compound **12b** was obtained from **11b** as a colorless oil in 97% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.24 (s, 3H, $SiCH_3$), 0.25 (s, 3H, $SiCH_3$), 1.01 (s, 9H, $3CH_3$), 1.81 (s, 3H, CH_3), 2.25 (d, 1H, $J=2.8$ Hz, OH), 2.31 (dd, 1H, $J=9.6$, 14.0 Hz, H^2), 2.51 (dd, 1H, $J=3.2$, 14.0 Hz, H^2), 3.77 (s, 3H, OMe), 4.87 (bs, 1H, H^4), 4.92 (bs, 1H, H^4), 5.11 (dt, 1H, $J=3.2$, 9.6, 2.8 Hz, H^1), 6.66 (dd, 1H, $J=8.8$, 2.8 Hz, H_{ar}), 6.71 (d, 1H, $J=8.8$ Hz, H_{ar}), 7.02 (d, 1H, $J=2.8$ Hz, H_{ar}); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ_C −4.2, −4.0, 18.1, 22.3, 25.8 (3C), 46.2, 55.6, 66.2, 111.7, 113.0, 113.7, 118.7, 135.0, 142.7, 145.9, 153.9; IR (film) ν 3472, 3074, 2956, 2931, 2858, 1495 cm^{-1}; MS-EI *m*/*z* (relative intensity) 322 (M^+, 1), 267 (24), 209 (39), 195 (36), 75 (44), 73 (100).

4.6.3. 3-Methyl-1-(2,5-di-*tert*-butyldimethylsilyloxyphenyl)but-3-en-1-ol 12c. Compound **12c** was obtained from **11c** as a colorless oil in 98% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.15 (s, 6H, $2SiCH_3$), 0.22 (s, 3H, $SiCH_3$), 0.23 (s, 3H, $SiCH_3$), 0.96 (s, 9H, $3CH_3$), 0.99 (s, 9H, $3CH_3$), 1.78 (s, 3H, CH_3), 2.24 (bs, 1H, OH), 2.29 (dd, 1H, $J=9.6$, 14.0 Hz, H^2), 2.47 (dd, 1H, $J=3.2$, 14.0 Hz, H^2), 4.84 (s, 1H, H^4), 4.89 (s, 1H, H^4), 5.05 (dd, 1H, $J=3.2$, 9.6 Hz, H^1), 6.57 (dd, 1H, $J=12.0$, 4.0 Hz, H_{ar}), 6.62 (d, 1H, $J=12.0$ Hz, H_{ar}), 6.89 (d, 1H, $J=4.0$ Hz, H_{ar}); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ_C −4.5 (2C), −4.1, −3.9, 18.1, 18.2, 22.4, 25.7 (6C), 46.2, 66.4, 113.7, 118.1, 118.5, 118.7, 134.9, 142.7, 146.4, 149.6; IR (film) ν 3489, 3075, 2956, 2930, 2858, 1488 cm^{-1}; MS-CI *m*/*z* (relative intensity) 422 (M^+, 21), 404 (100), 366 (81).

4.7. General procedure for oxidation of homoallylic alcohol 12a-c with Dess–Martin periodinane (DMP)

To a solution of alcohol **12a-c** (1.7 mmol) in DCM (10 mL) was added at 0 °C Dess–Martin Periodinane (1.06 g, 2.5 mmol). After 1 h, an aqueous solution of $NaHCO_3$ (10%) and $Na_2S_2O_3$ (10%) was added, the aqueous layer was extracted with DCM (3×20 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo to give the unstable ketone **13a-c** used without further purification.

4.7.1. 3-Methyl-1-(2-*tert*-butyldimethylsilyloxyphenyl)but-3-en-1-one 13a. Compound **13a** was obtained from **12a** as a colorless oil in 98% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 0.24 (s, 6H, $2SiCH_3$), 0.99 (s, 9H, $3CH_3$), 1.76 (s, 3H, CH_3), 3.70 (s, 2H, H^2), 4.78 (s, 1H, H^4), 4.90 (s, 1H, H^4), 6.82–7.51 (m, 4H, H_{ar}); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ_C −4.0 (2C), 18.3, 22.8, 25.8 (3C), 51.9, 114.7, 120.1, 121.1, 129.8, 131.5, 132.4, 139.5, 153.9, 201.6; IR (film) ν 2956, 2931, 2887, 2859, 1690, 1479, 1255, 910 cm^{-1}.

4.7.2. 3-Methyl-1-(5-methoxy-2-*tert*-butyldimethylsilyloxyphenyl)but-3-en-1-one 13b. Compound **13b** was obtained from **12b** as a colorless oil in 97% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 0.22 (s, 6H, $2SiCH_3$), 0.99 (s, 9H, $3CH_3$), 1.77 (s, 3H, CH_3), 3.72 (s, 2H, H^2), 3.77 (s, 3H, OMe), 4.79 (bs, 1H, H^4), 4.91 (bs, 1H, H^4), 6.76–7.03 (m, 3H, H_{ar}); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ_C −4.1 (2C), 18.3, 22.8, 25.8 (3C), 51.8, 55.6, 113.2, 114.7, 119.1, 121.2, 131.5, 139.6, 147.8, 153.6, 201.2; IR (film) ν 2956, 2931, 2859, 1684, 1490 cm^{-1}.

4.7.3. 3-Methyl-1-(2,5-di-*tert*-butyldimethylsilyloxyphenyl)but-3-en-1-one 13c. Compound **13c** was obtained from **12c** as a colorless oil in 96% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 0.15 (s, 6H, $2SiCH_3$), 0.20 (s, 6H, $2SiCH_3$), 0.96 (s, 9H, $3CH_3$), 0.97 (s, 9H, $3CH_3$), 1.75 (s, 3H, CH_3), 3.67 (s, 2H, H^2), 4.77 (s, 1H, H^4), 4.89 (s, 1H, H^4), 6.78–6.96 (m, 3H, H_{ar}); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ_C −4.5 (2C), −4.1 (2C), 18.1, 18.7, 22.8, 25.6 (3C), 25.8 (3C), 51.9, 114.7, 120.3, 120.7, 123.9, 131.8, 139.7, 148.1, 149.5, 202.5; IR (film) ν 2956, 2930, 2886, 2859, 1692, 1485, 1257, 909 cm^{-1}.

4.8. General procedure for enantioselective reduction of ketone 13a-c with CBS-oxazaborolidine

To a solution of ketone **13a-c** (1.7 mmol) and CBS-oxazaborolidine (0.17 mmol, 1 M in toluene) in anhydrous toluene (10 mL) at −60 °C under argon was added catecholborane (3.7 mmol, 1 M in THF). The reaction was stirred 16 h at this temperature and quenched with water (10 mL). The aqueous layer was extracted with EtOAc (3×10 mL), the combined organic layers were washed successively with an aqueous solution of $NaHCO_3$ (10%, 10 mL), an aqueous solution of HCl (1 N, 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography.

4.8.1. (−)-(1*S*)-3-Methyl-1-(2-*tert*-butyldimethylsilyloxyphenyl)but-3-en-1-ol 12a. Compound (−)-**12a** was obtained by reduction of **13a** using (*R*)-CBS-oxazaborolidine as a colorless oil in 72% yield; $[\alpha]_D^{20}$=−44.3 (*c*=1, acetone); ee=95%.

4.8.2. (+)-(1*R*)-3-Methyl-1-(2-*tert*-butyldimethylsilyloxyphenyl)but-3-en-1-ol 12a. Compound (+)-**12a** was obtained by reduction of **13a** using (*S*)-CBS-oxazaborolidine as a colorless oil in 75% yield; $[\alpha]_D^{20}$=+43.8 (*c*=1.1, acetone); ee=93%.

4.8.3. (−)-(1*S*)-3-Methyl-1-(5-methoxy-2-*tert*-butyldimethylsilyloxyphenyl)but-3-en-1-ol 12b. Compound (−)-**12b** was obtained by reduction of **13b** using (*R*)-CBS-oxazaborolidine as a colorless oil in 70% yield; $[\alpha]_D^{20}$=−40.7 (*c*=0.8, acetone); ee=90%.

4.8.4. (−)-(1*S*)-3-Methyl-1-(2,5-di-*tert*-butyldimethylsilyloxyphenyl)but-3-en-1-ol 12c. Compound (−)-**12c** was obtained by reduction of **13c** using (*R*)-CBS-oxazaborolidine as a colorless oil in 75% yield; $[\alpha]_D^{20}$=−38.7 (*c*=0.8, acetone); ee=84%.

4.9. Representative procedure for epoxidation of chiral homoallylic alcohols 12a-c and 19 with vanadium (IV) and *tert*-butylhydroperoxide

To a blue solution of homoallylic alcohol and vanadyl acetylacetonate (0.05 equiv.) in anhydrous dichloromethane, was added, at −5 °C under argon, *tert*-butyl hydroperoxide (5.5 M in nonane, 2 equiv.). The resulting red-brown solution was stirred at −5 °C for 3–5 h. Then, the reaction mixture was poured into 10% aqueous $Na_2S_2O_3$ and extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (7:3, petroleum ether/EtOAc) to provide **14** and **20** as a mixture of diastereomers.

4.9.1. (−)-(1*S*,3*R*)-3,4-Epoxy-3-methyl-1-(2-*tert*-butyldimethylsilyloxyphenyl)butan-1-ol 14a. Compound (−)-**14a** was obtained from (−)-**12a** as a colorless oil in 72% yield; $[\alpha]_D^{20}$=−46.2 (*c*=0.75, acetone); de=86%; major isomer ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.28 (s, 6H, $2SiCH_3$), 1.02 (s, 9H, $3CH_3$), 1.46 (s, 3H, CH_3), 1.74 (dd, 1H, *J*=14.4, 10.0 Hz, H^2), 2.16 (dd, 1H, *J*=14.4, 3.2 Hz, H^2), 2.59–2.65 (2d, 2H, *J*=4.8 Hz, H^4), 2.98 (d, 1H, *J*=3.6 Hz, OH), 5.31 (dt, 1H, *J*=3.2, 3.6, 10.0 Hz, H^1), 6.65–6.71 (m, 2H, H_{ar}), 7.01–7.05 (m, 2H, H_{ar}); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ_C −4.0 (2C), 18.3, 21.2 25.8 (3C), 43.7, 53.7, 56.3, 66.6, 118.1, 121.3, 126.8, 127.9, 134.3, 151.9; minor isomer ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.25 (s, 6H, $2SiCH_3$), 1.01 (s, 9H, $3CH_3$), 1.38 (s, 3H, CH_3), 1.90 (dd, 1H, *J*=14.8, 10.4 Hz, H^2), 2.23 (dd, 1H, *J*=14.8, 2.4 Hz, H^2), 2.70 (d, 1H, *J*=4.0 Hz, H^4), 3.05 (d, 1H, *J*=4.0 Hz, H^4), 3.25 (d, 1H, *J*=2.4 Hz, OH), 5.31 (dt, 1H, *J*=2.4, 2.4, 10.4 Hz, H^1), 6.65–7.05 (m, 4H, H_{ar}); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ_C −4.3 (2C), 18.3, 22.6 25.7 (3C), 42.0, 52.9, 57.2, 65.9, 117.9, 121.3, 126.6, 127.9, 134.0, 151.9; IR (film) ν 3457, 2956, 2930, 2859, 1488, 1254 cm^{-1}; MS-CI *m/z* (relative intensity) 308 (M^+,80), 291 (100).

4.9.2. (+)-(1*R*,3*S*)-3,4-Epoxy-3-methyl-1-(2-*tert*-butyldimethylsilyloxyphenyl)butan-1-ol 14a. Compound (+)-**14a** was obtained from (+)-**12a** as a colorless oil in 72% yield; $[\alpha]_D^{20}$=+44.2 (*c*=1.1, acetone); de=84%.

4.9.3. (−)-(1*S*,3*R*)-3,4-Epoxy-3-methyl-1-(5-methoxy-2-*tert*-butyldimethylsilyloxyphenyl)butan-1-ol 14b. Compound (−)-**14b** was obtained from (−)-**12b** as a colorless oil in 73% yield; $[\alpha]_D^{20}$=−42.7 (*c*=1.1, acetone); de=84%; major isomer ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.25 (s, 6H, $2SiCH_3$), 1.01 (s, 9H, $3CH_3$), 1.47 (s, 3H, CH_3), 1.68 (dd, 1H, *J*=14.8, 10.0 Hz, H^2), 2.17 (dd, 1H, *J*=14.8, 2.8 Hz, H^2), 2.60–2.66 (2d, 2H, *J*=4.8 Hz, H^4), 3.01 (d, 1H, *J*=3.2 Hz, OH), 3.76 (s, 3H, OMe), 5.28 (dt, 1H, *J*=3.2, 2.8, 10.0 Hz, H^1), 6.65–6.71 (m, 2H, $2H_{ar}$), 7.01–7.05 (m, 1H, H_{ar}); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ_C −4.0 (2C), 18.3, 21.2, 25.6 (3C), 43.8, 53.7, 55.6, 56.3, 66.7, 111.7, 113.3, 118.8, 135.2, 145.6, 154.1; minor isomer ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.22 (s, 6H, $2SiCH_3$), 0.97 (s, 9H, $3CH_3$), 1.38 (s, 3H, CH_3), 1.90 (dd, 1H, *J*=14.8, 10.4 Hz, H^2), 2.23 (dd, 1H, *J*=14.8, 2.4 Hz, H^2), 2.71 (d, 1H, *J*=4.0 Hz, H^4), 2.07 (d, 1H, *J*=4.0 Hz, H^4), 3.31 (d, 1H, *J*=2.4 Hz, OH), 3.77 (s, 3H, OMe), 5.02 (dt, 1H, *J*=2.4, 2.4,

10.4 Hz, H^1), 6.65–7.05 (m, 3H, H_{ar}); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ_C −4.0 (2C), 18.3, 22.7, 25.9 (3C), 41.8, 52.8, 55.6, 57.3, 66.0, 111.7, 113.3, 118.6, 134.8, 145.5, 154.1; IR (film) ν 3473, 2930, 2858, 1495 cm^{-1}; MS-CI *m/z* (relative intensity) 338 (M^+, 62), 321 (M−17, 100).

4.9.4. (−)-(1*S*,3*R*)-3,4-Epoxy-3-methyl-1-(2,5-di-*tert*-butyldimethylsilyloxyphenyl)butan-1-ol 14c. Compound (−)-**14c** was obtained from (−)-**12c** as a colorless oil in 70% yield; $[\alpha]_D^{20}$=−39.1 (*c*=1.0, acetone); de=82%; major isomer ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.16 (s, 6H, $2SiCH_3$), 0.24 (s, 6H, $2SiCH_3$), 0.96 (s, 9H, $3CH_3$), 1.01 (s, 9H, $3CH_3$), 1.45 (s, 3H, CH_3), 1.72 (dd, 1H, *J*=14.4, 10.0 Hz, H^2), 2.13 (dd, 1H, *J*=14.4, 3.2 Hz, H^2), 2.58–2.65 (2d, 2H, *J*=4.8 Hz, H^4), 2.91 (d, 1H, *J*=3.2 Hz, OH), 5.21 (dt, 1H, *J*=3.2, 3.2, 10.0 Hz, H^1), 6.58 (dd, 1H, *J*=8.8, 2.8 Hz, H_{ar}), 6.63 (d, 1H, *J*=8.8 Hz, H_{ar}), 6.90 (d, 1H, *J*=2.8 Hz, H_{ar}); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ_C −4.5 (2C), −4.0 (2C), 18.1, 18.3, 21.3, 25.7 (3C), 25.9 (3C), 43.8, 53.7, 56.3, 66.7, 118.2, 118.8, 118.9, 135.1, 146.1, 151.9; minor isomer ^1H NMR (400 MHz, $CDCl_3$): δ_H 0.16 (s, 6H, $2SiCH_3$), 0.23 (s, 6H, $2SiCH_3$), 0.96 (s, 9H, $3CH_3$), 0.98 (s, 9H, $3CH_3$), 1.38 (s, 3H, CH_3), 1.85 (dd, 1H, *J*=14.8, 10.0 Hz, H^2), 2.21 (dd, 1H, *J*=14.8, 2.4 Hz, H^2), 2.69 (d, 1H, *J*=4.0 Hz, H^4), 3.03 (d, 1H, *J*=4.0 Hz, H^4), 3.20 (d, 1H, *J*=2.4 Hz, OH), 4.99 (dt, 1H, *J*=2.4, 2.4, 10.0 Hz, H^1), 6.57–6.94 (m, 3H, H_{ar}); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ_C −4.3 (2C), −4.1 (2C), 18.1, 18.3, 22.7, 25.7 (3C), 25.9 (3C), 41.9, 52.9, 57.2, 66.0, 118.2, 118.8, 118.9, 134.8, 146.1, 151.8; IR (film) 3470, 2930, 2858, 1488 cm^{-1}; MS-CI *m/z* (relative intensity) 438 (M^+, 54), 421 (100).

4.10. General procedure for formation of 2*H*-1-benzopyran 3a-c

To a solution of epoxide **14a-c** (0.26 mmol) in THF (2 mL) was added at 0 °C TBAF (1 M in THF, 0.31 mmol). The reaction was stirred 1 h at room temperature and then hydrolyzed with a saturated aqueous solution of NH_4Cl (2 mL). The aqueous layer was extracted with EtOAc (3×10 mL), the organic layers were washed with brine (30 mL) and dried over $MgSO_4$, and concentrated in vacuo. The residue was dissolved in toluene (2 mL) and a catalytic amount of CSA (4 mol%) was added and the reaction was heated at 80 °C for 16 h. After cooling, a saturated aqueous solution of $NaHCO_3$ (1 mL) was added, the combined organic layer was dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (8:2, petroleum ether/EtOAc) to give the 2*H*-1-benzopyran **3a-c**.

4.10.1. (−)-2-Hydroxymethyl-2-methyl-2*H*-1-benzopyran 3a. Compound (−)-**3a** was obtained from (−)-**14a** as a colorless oil in 80% yield; $[\alpha]_D^{20}$=−13.4 (*c*=0.4, acetone); ee=44%; ^1H NMR (200 MHz, $CDCl_3$): δ 1.36 (s, 3H, CH_3), 2.03 (bs, 1H, OH), 3.59 (d, 1H, *J*=11.6 Hz, $H^{1'}$), 3.68 (d, 1H, *J*=11.6 Hz, $H^{1'}$), 5.56 (d, 1H, *J*=9.9 Hz, H^3), 6.45 (d, 1H, *J*=9.9 Hz, H^4), 6.76–7.15 (m, 4H, H_{ar}); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 22.6, 68.7, 79.2, 116.1, 120.8, 121.1, 124.7, 126.6, 126.7, 129.3, 153.9; IR (film) ν 3396, 2972, 2927, 1486, 1240, 1053, 773 cm^{-1}; MS-EI *m/z* (relative intensity) 176 (M^+, 3), 145 (100), 115 (13), 91 (5). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found C, 74.82; H, 6.91.

4.10.2. (+)-2-Hydroxymethyl-2-methyl-2*H*-1-benzopyran 3a. Compound (+)-**3a** was obtained from (+)-**14a** as a colorless oil in 80% yield; $[\alpha]_D^{20}$=+13.0 (*c*=0.5, acetone); ee=46%.

4.10.3. (−)-2-Hydroxymethyl-6-methoxy-2-methyl-2*H*-1-benzopyran 3b. Compound (−)-**3b** was obtained from (−)-**14b** as a colorless oil in 75% yield; $[\alpha]_D^{20}$=−10.2 (*c*=0.4, acetone); ee=43%; ^1H NMR (200 MHz, $CDCl_3$): δ 1.35 (s, 3H, CH_3), 2.03 (bs, 1H, OH), 3.58 (d, 1H, *J*=11.8 Hz, $H^{1'}$), 3.67 (d, 1H, *J*=11.8 Hz, $H^{1'}$), 3.75 (s, 3H, OCH_3), 5.62 (d, 1H, *J*=10.0 Hz, H^3), 6.42 (d, 1H, *J*=10.0 Hz, H^4), 6.56 (d, 1H, *J*=2.8 Hz, H_{ar}), 6.67 (dd, 1H, *J*=2.8, 8.8 Hz, H_{ar}), 6.73 (d, 1H, *J*=8.8 Hz, H_{ar}); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 22.3, 55.7, 68.5, 79.0, 111.8, 114.5, 116.7, 121.5, 124.9, 127.9, 146.2, 154.0; IR (film) ν 3432, 2932, 2834, 1492, 1040 cm^{-1}; MS-EI *m/z* (relative intensity) 206 (M^+, 5), 175 (100), 132 (18); anal.calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.86. Found C, 69.95; H, 6.80.

4.10.4. (−)-2-Hydroxymethyl-6-hydroxy-2-methyl-2*H*-1-benzopyran 3c. Compound (−)-**3c** was obtained from (−)-**14c** as a colorless oil in 68% yield; $[\alpha]_D^{20}$=−7.6 (*c*=0.3, acetone); ee=35%; ^1H NMR (200 MHz, $CDCl_3$): δ 1.35 (s, 3H, CH_3), 3.58 (d, 1H, *J*=11.6 Hz, $H^{1'}$), 3.68 (d, 1H, *J*=11.6 Hz, $H^{1'}$), 5.61 (d, 1H, *J*=9.6 Hz, H^3), 6.38 (d, 1H, *J*=9.6 Hz, H^4), 6.50 (d, 1H, *J*=2.8 Hz, H_{ar}), 6.59 (dd, 1H, *J*=2.8, 8.4 Hz, H_{ar}), 6.68 (d, 1H, *J*=8.4 Hz, H_{ar}); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 22.3, 68.4, 79.3, 111.8, 114.8, 116.4, 121.5, 124.2, 127.8, 146.6, 154.2; IR (film) ν 3432, 2932, 2834, 1492, 1040 cm^{-1}; MS-CI *m/z* (relative intensity) 210 (M+18, 100), 192 (M^+, 51). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found C, 68.82; H, 6.36.

4.11. 2-Tosylaminobenzaldehyde 18

To a solution of 2-aminobenzaldehyde (2.8 g, 23.3 mmol) and pyridine (4.1 mL, 51.3 mmol) in anhydrous dichloromethane (30 mL) was added, dropwise at room temperature under argon, a solution of *para*-toluenesulfonyl chloride (4.8 g, 25.6 mmol) in dry dichloromethane (20 mL). The resulting mixture was stirred for 20 h, poured into water (80 mL) and extracted with dichloromethane (3×50 mL). The combined organic layers were washed with saturated aqueous $CuSO_4$ (100 mL), brine (100 mL) and dried over $MgSO_4$. After concentration in vacuo the crude residue was triturated with a mixture of 8:2 petroleum ether/ethyl acetate (20 mL), filtered over celite, concentrated under vacuum and purified by column chromatography on silica gel (8:2, petroleum ether/EtOAc) to provide **18** (4.48 g, 70%) as a pale yellow solid; mp 128 °C; ^1H NMR (200 MHz, $CDCl_3$) δ_H 2.36 (s, 3H, CH_3), 7.12–7.26 (m, 4H, H_{ar}), 7.51–7.79 (m, 4H, H_{ar}), 9.82 (s, 1H, CHO), 10.80 (s, 1H, NHTs); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ_C 21.4, 117.7, 121.7, 122.9, 127.1 (2C), 129.7 (2C), 135.7, 136.0, 136.2, 139.1, 144.1, 195.0; IR (KBr) ν 1662, 1602, 1493 cm^{-1}; MS-EI *m/z* (relative intensity) 275 (M^+, 10), 120 (100), 91 (50), 65 (33), 39 (12).

4.12. Preparation of chiral homoallylic alcohols 19

Homoallylic alcohols **19** were prepared according to Section 4.5.

4.12.1. (−)-(*R*)-Methyl-1-(2-tosylaminophenyl)but-3-en-1-ol (−)-19. Compound (−)-(*R*)-**19** was obtained from **18** and **9** (prepared with (+)-DIP-Cl) as a pale yellow solid in 80% yield: mp 79 °C; $[\alpha]_D^{20}=-16.7$ (c=1.0, acetone); ee=84%; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.69 (s, 3H, CH_3), 2.19 (dd, 1H, J=4, 14 Hz, H^2), 2.28 (dd, 1H, J=10, 14 Hz, H^2), 2.37 (s, 3H, CH_3), 2.56 (bs, 1H, OH), 4.68 (dd, 1H, J=10, 4 Hz, H^1), 4.75 (s, 1H, H^4), 4.92 (s, 1H, H^4), 7.02–7.72 (m, 8H, H_{ar}), 8.57 (s, 1H, NH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 21.4, 22.0, 45.1, 71.3, 114.6, 121.7, 124.4, 127.0 (2C), 127.5, 128.4, 129.5 (2C), 132.0, 135.8, 136.9, 141.3, 143.6; IR (KBr) ν 3491, 3239, 2922, 1159 cm^{-1}; MS-EI m/z (relative intensity) 276 (35), 91 (100), 65 (35).

4.12.2. (+)-(*S*)-Methyl-1-(2-tosylaminophenyl)but-3-en-1-ol (+)-19. Compound (+)-(*S*)-**19** was obtained from **18** and **9** (prepared with (−)-DIP-Cl) as a pale yellow solid in 84% yield: mp 79 °C; $[\alpha]_D^{20}=+17.0$ (c=1.0, acetone); ee=82%.

4.13. Preparation of epoxide 20

Epoxides **20** were prepared according to Section 4.9.

4.13.1. (−)-(1*R*,3*S*)-3,4-Epoxy-3-methyl-1-(2-tosylamino-phenyl)butan-1-ol (−)-20. Compound (−)-(1*R*,3*S*)-**20** was obtained from (−)-(*R*)-**19** (250 mg, 754 μmol) as a colorless oil (252 mg, 96%); $[\alpha]_D^{20}=-13.9$ (c=0.6, acetone); de=84%; ^{1}H NMR (200 MHz, $CDCl_3$); major isomer δ_H 1.33 (s, 3H, CH_3), 1.72 (dd, 1H, J=9.4, 14.6 Hz, H^2), 1.86 (dd, 1H, J=3.5, 14.6 Hz, H^2), 2.38 (s, 3H, CH_3), 2.57 (d, 1H, J=4.6 Hz, H^4), 2.61 (d, 1H, J=4.6 Hz, H^4), 3.70 (bs, 1H, OH), 4.99 (dd, 1H, J=3.5, 9.4 Hz, H^1), 6.99–7.72 (m, 8H, H_{ar}), 8.67 (s, 1H, NH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 21.1, 21.4, 42.2, 54.3, 56.2, 71.6, 122.0, 124.6, 127.1 (2C), 127.3, 128.5, 129.6 (2C), 132.7, 135.8, 137.1, 143.6; minor isomer (meaningful signals) δ_H 2.73 (d, 1H, J=3.7 Hz, H^4), 3.04 (d, 1H, J=3.7 Hz, H^4), 4.67 (dd, 1H, J=3.5, 9.4 Hz, H^1); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 40.3, 52.2, 57.4, 71.3; IR (film) ν 3474, 3239, 2925, 1161 cm^{-1}; MS-EI m/z (relative intensity) 248 (8), 192 (25), 174 (20), 132 (100), 91 (24); MS-CI m/z (relative intensity) 364 (100), 347 (95).

4.13.2. (+)-(1*S*,3*R*)-3,4-Epoxy-3-methyl-1-(2-tosylaminophenyl)butan-1ol (+)-20. Compound (+)-(1*S*,3*R*)-**20** was obtained from (+)-(*S*)-**19** (600 mg, 1.81 mmol) as a colorless oil (560 mg, 89%); $[\alpha]_D^{20}=+10.8$ (c=1.0, acetone); de=82%.

4.14. Typical procedure for formation of compounds 4

To a solution of epoxide **20** in anhydrous toluene (25 mL) at room temperature under argon was added slowly trifluoroacetic acid (2 equiv.) and the solution was stirred for 16 h. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ (4 mL). The resulting mixture was poured into water (20 mL) and extracted with diethyl ether (3×20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (7:3, petroleum ether/EtOAc) to provide two diastereomers.

4.14.1. (−)-*trans*-(2*S*,4*R*)-2-(Hydroxymethyl)-2-methyl-1-tosyl-1,2,3,4-tetrahydroquinolin-4-ol (−)-4. Compound (−)-*trans*-(2*S*,4*R*)-**4** was obtained from (−)-(1*R*,3*S*)-**20** (220 mg, 0.63 mmol) as a colorless oil (64 mg, 29%); $[\alpha]_D^{20}=-3.0$ (c=0.5, acetone); ee=94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.43 (s, 3H, CH_3), 1.83 (dd, 1H, J=13, 11 Hz, H^3), 2.14 (dd, 1H, J=13, 5 Hz, H^3), 2.35 (s, 3H, CH_3), 3.90 (s, 2H, CH_2), 5.02 (dd, 1H, J=11, 5 Hz, H^4), 6.98–7.70 (m, 8H, H_{ar}); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ_C 21.5, 25.0, 47.3, 78.2, 80.1, 80.3, 121.6, 124.4, 127.0 (2C), 127.1, 128.5, 129.6 (2C), 130.4, 136.0, 137.2, 143.6; IR (film) ν 3492, 3254, 2967, 2928, 2880, 1592, 1499, 1453, 1334, 1159 cm^{-1}; MS-EI m/z (relative intensity) 347 (M$^+$, 3), 274 (17), 192 (25), 174 (80), 144 (42), 118 (100), 117 (43), 91 (72), 65 (36), 39 (16); MS-CI m/z (relative intensity) 365 (M+NH_3, 18), 348 (MH$^+$, 100), 330 (61), 291 (37), 274 (69), 144 (21). Anal. Calcd for $C_{18}H_{21}O_4NS$: C, 62.18; H, 6.04; S, 9.21; N, 4.03. Found: C, 62.90; H, 6.34; S, 9.25; N, 4.05.

4.14.2. (−)-*cis*-(2*R*,4*R*)-2-(Hydroxymethyl)-2-methyl-1-tosyl-1,2,3,4-tetrahydroquinolin-4-ol (−)-4. Compound (−)-*cis*-(2*R*,4*R*)-**4** was obtained from (−)-(1*R*,3*S*)-**20** (220 mg, 0.63 mmol) as a white solid (64 mg, 29%); $[\alpha]_D^{20}=-4.0$ (c=0.2, acetone); ee=63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.52 (s, 3H, CH_3), 1.5–1.6 (m, 4H, H^3, CH_3), 1.89 (dd, 1H, J=14, 6 Hz, H^3), 2.01 (d, 1H, J=6 Hz, OH), 2.40 (s, 3H, CH_3), 2.85 (bt, 1H, J=6 Hz, OH), 3.52 (dd, 1H, J=12, 6 Hz, H$^{2'}$), 3.63 (dd, 1H, J=12, 6 Hz, H$^{2'}$), 4.54 (dd, 1H, J=12, 6 Hz, H^4), 7.21–7.34 (m, 8H, H_{ar}); IR (KBr) ν 3300, 3024, 2957, 2925, 2852, 1599, 1481, 1454, 1350, 1159, 1090 cm^{-1}; MS-EI m/z (relative intensity) 347 (1), 316 (20), 155 (12), 144 (100), 91 (41), 77 (13), 65 (19). Anal. Calcd for $C_{18}H_{21}O_4NS$: C, 62.18; H, 6.04; S, 9.21; N, 4.03. Found: C, 63.20; H, 6.38; S, 9.15; N, 4.05.

4.14.3. (+)-*trans*-(2*R*,4*S*)-2-(Hydroxymethyl)-2-methyl-1-tosyl-1,2,3,4-tetrahydroquinolin-4-ol (+)-4. Compound (+)-*trans*-(2*R*,4*S*)-**4** was obtained from (+)-(1*S*,3*R*)-**20** (300 mg, 0.86 mmol) as a colorless oil (68 mg, 23%); $[\alpha]_D^{20}=+2.8$ (c=0.3, acetone); ee=88%. Anal. Calcd for $C_{18}H_{21}O_4NS$: C, 62.18; H, 6.04; S, 9.21; N, 4.03. Found: C, 62.19; H, 6.05; S, 9.21; N, 4.03.

4.14.4. (+)-*cis*-(2*S*,4*S*)-2-(Hydroxymethyl)-2-methyl-1-tosyl-1,2,3,4-tetrahydroquinolin-4-ol (+)-4. Compound (+)-*cis*-(2*S*,4*S*)-**4** was obtained from (+)-(1*S*,3*R*)-**20** (300 mg, 0.86 mmol) as a white solid (66 mg, 22%); $[\alpha]_D^{20}=+2.0$ (c=0.2, acetone); ee=40%. Anal. Calcd for $C_{18}H_{21}O_4NS$: C, 62.18; H, 6.04; S, 9.21; N, 4.03. Found: C, 62.20; H, 6.04; S, 9.21; N, 4.08.

4.15. Formation of the acetonide

4.15.1. 3-Methyl-1-phenylbut-3-en-1-ol 21. To a solution

of 2-methylpropene magnesium chloride (0.6 M in THF, 6 mmol) at −30 °C was added dropwise a solution of benzaldehyde (530 mg, 0.5 mmol) in THF (10 mL). The reaction was stirred 1 h at room temperature and then quenched with a saturated aqueous solution of NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (2×20 mL), the organic layers were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (9:1, petroleum ether/EtOAc) to give a colorless oil (794 mg, 98% yield); ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.78 (s, 3H, CH_3), 2.25 (bs, 1H, OH), 2.41 (d, 2H, J=6.4 Hz, H^2), 4.78 (t, 1H, J=6.4 Hz, H^1), 4.81–4.91 (m, 2H, H^4), 7.23–7.36 (m, 5H, H_{ar}); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ_C 22.3, 48.2, 71.3, 114.0, 125.7 (2C), 127.4, 128.3 (2C), 142.3, 144.0; IR (film) ν 3396, 3073, 3030, 2969, 2936, 1454, 700 cm^{-1}; MS-CI *m/z* (relative intensity) 180 (M+18, 26), 162 (M^+, 100), 145 (37).

4.15.2. 3,4-Epoxy-3-methyl-1-phenylbutan-1-ol 22. To a blue solution of homoallylic alcohol **21** (1.3 mmol, 620 mg) and vanadyl acetylacetonate (131 μmol, 35 mg) in anhydrous dichloromethane, was added, at −5 °C under argon, *tert*-butyl hydroperoxide (5.5 M in nonane, 0.47 mL, 2.6 mmol). The resulting red-brown solution was stirred at 0 °C for 5 h. Then, the reaction mixture was poured into 10% aqueous $Na_2S_2O_3$ and extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (7:3, petroleum ether/EtOAc) to provide **22** (180 mg, 78% yield) as a mixture of diastereomers (ratio 8:2); major isomer ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.44 (s, 3H, CH_3), 2.00 (m, 2H, H^2), 2.60 (m, 2H, H^4), 3.05 (bs, 1H, OH), 4.95 (m, 1H, H^1), 7.25–7.35 (m, 5H, H_{ar}); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ_C 21.2, 45.3, 53.9, 56.2, 71.5, 125.6 (2C), 127.5, 128.4 (2C), 144.0; minor isomer ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.39 (s, 3H, CH_3), 2.03 (m, 2H, H^2), 2.87 (m, 2H, H^4), 3.32 (bs, 1H, OH), 4.74 (m, 1H, H^1), 7.25–7.35 (m, 5H, H_{ar}); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ_C 22.6, 43.8, 52.9, 57.1, 71.1, 125.6 (2C), 127.5, 128.4 (2C), 143.6; IR (film) ν 3438, 2927, 1071, 760, 701 cm^{-1}; MS-CI *m/z* (relative intensity) 196 (M+18, 75), 178 (M^+, 48), 161 (M−17).

4.15.3. 3,4-Epoxy-3-methyl-1-phenyl-1-*tert*-butyldimethylsilyloxybutane 23. To a solution of **22** (620 mg, 3.5 mmol), imidazole (473 mg, 7.0 mmol) in DMF (4 mL) was added *tert*-butyldimethylsilyl chloride (780 mg, 5.2 mmol). The reaction was heated 18 h at room temperature, then 50 mL of water and 50 mL of EtOAc were added. The aqueous layer was extracted with ethyl acetate (3×40 mL), the organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (9:1, petroleum ether/EtOAc) to give the compound **23** (880 mg, 86% yield) as a mixture of diastereomers (ratio 8:2); major isomer ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 0.17 (s, 3H, $SiCH_3$), 0.41 (s, 3H, $SiCH_3$), 1.25 (s, 9H, $3CH_3$), 1.68 (s, 3H, CH_3), 2.06 (m, 1H, H^2), 2.66 (m, 1H, H^2), 2.79 (m, 2H, H^4), 5.14 (m, 1H, H^1), 7.63–7.69 (m, 5H, H_{ar}); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ_C −4.5 (2C), 18.0, 22.2, 25.8 (3C), 47.9, 53.5, 55.1, 72.9, 125.9 (2C), 127.3, 128.1 (2C), 144.9; minor isomer ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 0.13 (s, 3H, $SiCH_3$), 0.37 (s, 3H, $SiCH_3$), 1.25 (s, 9H, $3CH_3$), 1.79 (s, 3H, CH_3), 2.04 (m, 1H, H^2), 2.40 (m, 1H, H^2), 2.97 (m, 2H, H^4), 5.21 (m, 1H, H^1), 7.63–7.69 (m, 5H, H_{ar}); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ_C −5.0 (2C), 18.0, 21.3, 25.8 (3C), 48.5, 54.9, 55.3, 72.9, 125.8 (2C), 127.3, 128.1 (2C), 144.9; IR (film) ν 2956, 2929, 2857, 1092, 837 cm^{-1}; MS-CI *m/z* (relative intensity) 293 (M+1, 5), 221 (100), 161 (19), 132 (30).

4.15.4. 2-Methyl-1,4-diphenyl-4-*tert*-butyldimethylsilyloxybutan-2-ol 24. To a solution of $BF_3{\cdot}Et_2O$ (4 mmol), in THF (4 mL) was added at −78 °C phenyllithium (1.4 M, 2.8 mL, 4.0 mmol). Then, a solution of epoxide **23** (292 mg, 1 mmol) in THF (2 mL) was added quickly and the reaction was stirred 2 h at −60 °C. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (25 mL), the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (9:1, petroleum ether/EtOAc) to give the compound **24** (274 mg, 74% yield) as a mixture of diastereoisomers (ratio 8:2); major isomer ^{1}H NMR (200 MHz, $CDCl_3$): δ_H −0.19 (s, 3H, $SiCH_3$), 0.26 (s, 3H, $SiCH_3$), 1.07 (s, 9H, $3CH_3$), 1.54 (s, 3H, CH_3), 1.90 (m, 1H, H^3), 2.23 (m, 1H, H^3), 2.97 (bs, 2H, H^1), 4.60 (bs, 1H, OH), 5.19 (m, 1H, H^4), 7.40–7.51 (m, 10H, H_{ar}); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ_C −4.1 (2C), 17.8, 25.8 (3C), 28.2, 46.9, 50.2, 72.7, 74.7, 126.1, 127.1 (2C), 127.8 (2C), 128.1 (2C), 128.7, 130.7 (2C), 137.7, 144.6; minor isomer ^{1}H NMR (200 MHz, $CDCl_3$): δ_H −0.13 (s, 3H, $SiCH_3$), 0.33 (s, 3H, $SiCH_3$), 1.12 (s, 9H, $3CH_3$), 1.26 (s, 3H, CH_3), 1.84 (m, 1H, H^3), 2.27 (m, 1H, H^3), 3.05 (d, 1H, J=13.2 Hz, H^1), 3.26 (d, 1H, J=13.2 Hz, H^1), 4.53 (bs, 1H, OH), 5.39 (m, 1H, H^4), 7.40–7.51 (m, 10H, H_{ar}); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ_C −4.9 (2C), 17.8, 25.8 (3C), 28.2, 46.9, 49.1, 72.7, 74.7, 126.4, 127.1 (2C), 127.8 (2C), 128.1 (2C), 128.7, 130.4 (2C), 138.2, 144.6; MS-CI *m/z* (relative intensity) 388 (M+18, 5), 370 (M^+, 30), 238 (100).

4.15.5. 3-Methyl-1,4-diphenylbutan-1,3-diol 25. To a solution of **24** (290 mg, 0.78 mmol) in THF (2 mL) was added at 0 °C TBAF (1 M in THF, 0.86 mmol). The reaction was stirred 1 h at room temperature and then hydrolysed with a saturated aqueous solution of NH_4Cl (2 mL). The aqueous layer was extracted with EtOAc (3×10 mL), the organic layers were washed with brine (30 mL) and dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (7:3, petroleum ether/EtOAc) to give the compound **25** as a white solid (189 mg, 95% yield) as a mixture of diastereomers (ratio 8:2); mp 117 °C; major isomer ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.35 (s, 3H, CH_3), 1.67 (d, 1H, J=14.2 Hz, H^2), 1.93 (dd, 1H, J=14.2, 11.0 Hz, H^2), 2.73 (d, 1H, J=13.6 Hz, H^4), 2.78 (d, 1H, J=13.6 Hz, H^4), 3.06 (bs, 1H, OH), 4.05 (bs, 1H, OH), 5.00 (d, 1H, J=11.0 Hz, H^1), 7.16–7.35 (m, 10H, H_{ar}); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ_C 25.3, 48.5, 50.3, 71.8, 73.5, 125.6 (2C), 126.5 (2C), 127.3, 128.1 (2C), 128.3 (2C), 130.5, 136.6, 144.5; minor isomer (meaningful signals) ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.12 (s, 3H, CH_3), 1.85 (m, 2H, H^2), 2.84 (d, 1H, J=13.2 Hz, H^4), 3.09 (d, 1H, J=13.2 Hz, H^4), 3.06 (bs, 1H, OH), 4.05 (bs, 1H, OH), 5.18 (m, 1H, H^1), 7.16–7.35 (m, 10H, H_{ar}); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ_C 28.7, 46.2, 49.1, 71.6, 73.6, 125.5 (2C), 126.4 (2C), 127.3, 128.2 (2C), 128.4 (2C), 130.4, 137.3, 144.6; IR (film) ν 3334, 3028, 2971, 2913,

700 cm^{-1}; MS-CI *m/z* (relative intensity) 274 (M+18, 62), 256 (M^+, 6), 238 (100), 221 (74).

4.15.6. 4-Benzyl-2,2,4-trimethyl-6-phenyl-1,3-dioxacyclohexane 26. To a solution of diol **25** (100 mg, 0.39 mmol) in 2,2-dimethoxypropane (3.5 mL) was added at rt CSA (2 mol%). After 1 h the reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (4 mL). The aqueous layer was extracted with EtOAc (3×10 mL), the combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (9:1, petroleum ether/EtOAc) to give compound **26** as a white solid (106 mg, 92% yield) as a mixture of diastereomers (ratio 8:2); mp 56 °C; major isomer ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.41 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.54 (dd, 1H, *J*=2.0, 12.0 Hz, H^5), 1.56 (s, 3H, CH_3), 1.76 (dd, 1H, *J*=11.6, 12.0 Hz, H^5), 2.76 (d, 1H, *J*=12.0 Hz, PhC*H*), 2.81 (d, 1H, *J*=12.0 Hz, PhC*H*), 4.90 (dd, 1H, *J*=2.0, 11.6 Hz, H^6), 7.21–7.33 (m, 10H, H_{ar}); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ_C 25.1, 25.7, 31.9, 41.7, 51.6, 68.0, 73.5, 99.0, 125.9 (2C), 126.2, 127.4, 127.7 (2C), 128.4 (2C), 130.9 (2C), 137.3, 142.5; minor isomer ^1H NMR (200 MHz, $CDCl_3$): δ_H 1.24 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.62–2.10 (m, 2H, H^5), 2.90 (d, 1H, *J*=13.6 Hz, PhC*H*), 3.16 (d, 1H, *J*=13.6 Hz, PhC*H*), 4.84 (m, 1H, H^6), 7.21–7.33 (m, 10H, H_{ar}); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ_C 26.8, 30.4, 31.7, 41.3, 47.5, 68.4, 74.1, 99.0, 125.5 (2C), 126.3, 127.4, 127.9 (2C), 128.4 (2C), 130.6 (2C), 138.0, 142.5; IR (film) ν 2990, 2938, 699 cm^{-1}; MS-CI *m/z* (relative intensity) 314 (M+18, 4), 296 (M^+, 1), 238 (86), 152 (100).

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