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# Two-way enantioselective control in the epoxidation of alkenes with the keto bile acid–Oxone® system

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**Abstract**—A number of 3-keto bile acid derivatives has been prepared and evaluated in the asymmetric epoxidation of unfunctionalized olefins with Oxone. The control of the enantioselectivity with the production of both enantiomers is strictly regulated by the bile acid inductor, as a function of substitution at carbons C(7) or C(12). Up to 98% ee has been achieved. The stereochemical outcome of the reaction may be rationalized in terms of spiro transition state model.

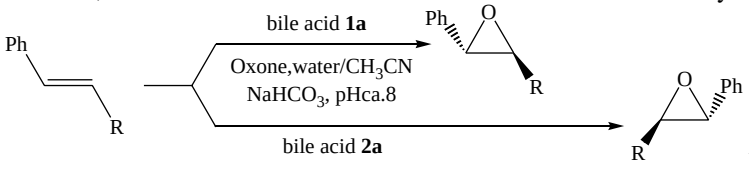

## 1. Introduction

Optically active epoxides are useful chiral synthons in organic synthesis and various chemical and biological methods have been developed for the preparation of these derivatives.[1] The asymmetric epoxidation of alkenes represents the most direct approach to these compounds[2] and impressive results have been achieved by many research groups in the epoxidation of allylic alcohols,[3] non-activated olefins[4,5] and in the nucleophilic epoxidation of electron-poor alkenes.[6,7] Chiral dioxiranes embody a new generation of enantioselective oxidants for olefin epoxidation[8] and *vic*-diol oxidation.[8c] These non-metal peroxidic oxygen transferring agents are readily prepared from suitable optically active ketones and potassium monoperoxysulfate (Oxone®) under buffered and mild conditions.

The epoxidation is stereospecific and occurs using the in situ generated dioxiranes both in stoichiometric and catalytic conditions.[8] Since the first report by Curci et al.[9] utilizing an optically active butanone derivative, various chiral ketones have been investigated by many laboratories and considerably high enantiomeric excess values have been reported for terminal, trans- and cis-disubstituted and trisubstituted alkenes, as well as for functionalized carbon–carbon double bonds.[8] In particular, the high enantioselective epoxidation of styrenes represented an important challenge for many research groups, with results ranging from good to excellent.[10]

With this background and based on our recent work, we have reported that bile acid-derived ketones **1** of Chart 1, in association with Oxone, served as efficient oxidant in the asymmetric epoxidation of electron-poor[11] and simple olefins.[12]

In this epoxidation procedure, the control of the sense of the enantioselection was strictly regulated by the bile acid inductor, as a function of substitution at carbons C(7) or C(12) of the steroidal framework. As an example, in the epoxidation of cinnamic acid derivatives, specific and stereochemically appropriate C(7) substitution led to the formation of (−) epoxides of (2*R*,3*S*) absolute configuration,[13] whereas C(12) substituted bile acids promote the formation of the opposite (+)-(2*S*,3*R*) epoxides **2** of Chart 1.[11,13] This important stereochemical control has also been found in the oxidation of mono-, trans-, *gem*-disubstituted and trisubstituted unfunctionalized alkenes,[12] with a systematic inversion of the epoxide configuration by




(1)

*Keywords*: Enantioselective epoxidation; Oxone; Bile acids; Chiral dioxiranes.
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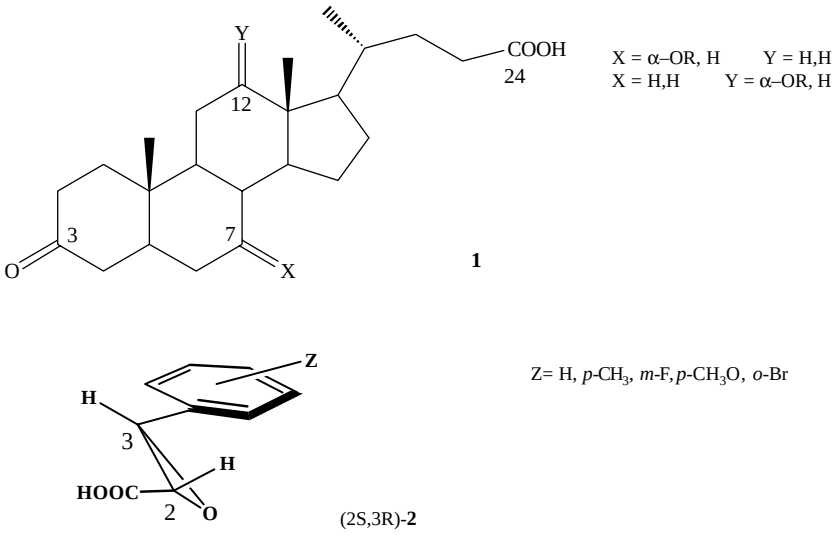
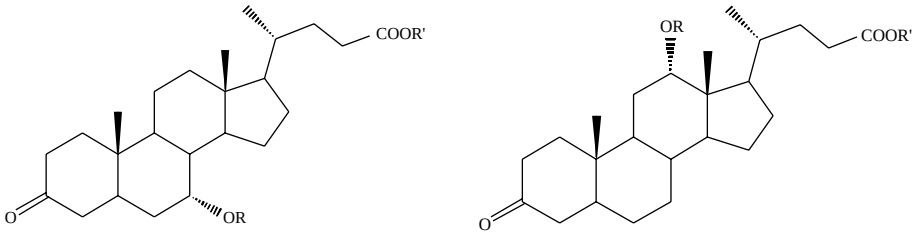



**Chart 1.** Bile acid-derived ketones **1** and (2*S*,3*R*)-cinnamic acid epoxides **2**.

changing the position of the C(7)/C(12) substituent on **1**, (Eq. 1).

As part of our efforts to understand the structural requirements and factors involved in this asymmetric epoxidation, we have synthesized some new **1**-type bile acid derivatives all having a C(3) carbonyl function and substituents at C(7) or C(12) of different polarity and bulkiness. In addition, the stereochemical outcome of the



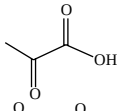
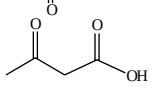
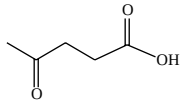
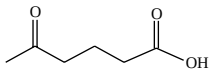
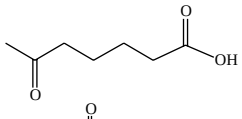
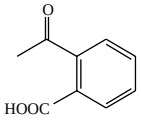

| 7-substituted bile acid | R | R' | 12-substituted bile acid |
|---|---|---|---|
| **3a** | H | H | **4a** |
| **3b** |  | $CH_3$ | **4b** |
| **3c** |  | $CH_3$ | **4c** |
| **3d** |  | H | -- |
| -- | | $CH_3$ | **4d** |
| **3e** |  | $CH_3$ | **4e** |
| **3f** |  | $CH_3$ | **4f** |
| **3g** |  | $CH_3$ | **4g** |
| **3h** | | H | **4h** |

**Chart 2.** 3-Keto-5-β-cholan-24-oic acids investigated in this study.

reaction has been rationalized with the help of the spiro transition state model.[8a]

## 2. Results and discussion

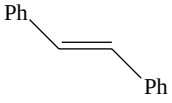
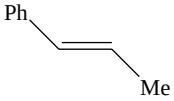
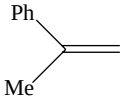
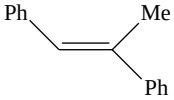
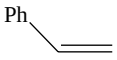
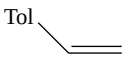
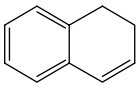
### 2.1. Epoxidation studies

The systematic study of the role played by the C(7)/C(12) substituent characteristics and steric size was carried out by preparing the ketones **3a–h** and **4a–h**, and by investigating their performances with respect to enantioselectivity. Ketones **3a–h** and **4a–h**, shown in Chart 2, are readily obtained from common, low cost and commercially available bile acids by adapting literature procedures.

The structure of the bile acids is characterized by a remarkable robustness and rigidity that prevents any distortion, thus maintaining the chiral elements of the carbonyl function also after its conversion into dioxirane. The epoxidation reaction was carried out in water–$CH_3CN$ (1/1) EDTA, pH ca. 8 using equimolar concentrations of substrate and bile acid in the presence of an excess of Oxone. The results of the epoxidation of various alkenes are shown in Table 1.

With all substrates the epoxidation is complete in 12 h at 0 °C, with enantiomeric excesses varying from excellent

**Table 1**. Asymmetric epoxidation of selected unfunctionalized alkenes with Oxone in the presence of 3-keto-7-substituted and 3-keto-12-substituted bile acids[a]

| Substrate | 7-Substituted bile acids | | | | 12-Substituted bile acids | | | |
|---|---|---|---|---|---|---|---|---|
| | | Yield (%) | ee (%) | Absolute configuration | | Yield (%) | ee (%) | Absolute configuration |
|  | **1a** | 90 | 54 | (−)-(*S*,*S*)[18] | **2a** | 55 | 43 | (+)-(*R*,*R*)[18] |
| | **1b** | 90 | 80 | | **2b** | 90 | 90 | |
| | **1c** | 60 | 80 | | **2c** | 45 | 80 | |
| | **1d** | 92 | 40 | | **2d** | 45 | 60 | |
| | **1e** | 70 | 80 | | **2e** | 45 | 85 | |
| | **1f** | 60 | 70 | | **2f** | 40 | 70 | |
| | **1g** | 80 | 60 | | **2h**[b] | 50 | 98 | |
|  | **1a** | 99 | 37 | (−)-(*S*,*S*)[19] | **2a** | 80 | 15 | (+)-(*R*,*R*)[19] |
| | **1b**[c] | 25 | 70 | | **2b**[c] | 50 | 70 | |
| | **1c** | 99 | 70 | | **2c** | 70 | 50 | |
| | **1d** | 60 | 47 | | **2d**[d] | 10 | 78 | |
| | **1e**[e] | 40 | 60 | | **2e** | 99 | 65 | |
| | **1f** | 95 | 60 | | **2f**[f] | 30 | 55 | |
| | **1g** | 40 | 70 | | **2h** | 20 | 66 | |
|  | **1a** | 99 | 33 | (+)-*S*[20] | **2a** | 75 | 41 | (−)-*R*[20] |
| | **1b** | 99 | 50 | | **2b** | 99 | 76 | |
| | **1c** | 60 | 55 | | **2c** | 70 | 65 | |
| | **1d** | 98 | 50 | | **2d** | 70 | 45 | |
| | **1e** | 99 | 57 | | **2e** | 99 | 65 | |
| | **1f** | 60 | 50 | | **2f** | 70 | 40 | |
| | **1g** | 40 | 30 | | **2h** | 40 | 65 | |
|  | **1a** | 50 | 49 | (−)-(*S*,*S*)[21] | **2a** | 75 | 44 | (+)-(*R*,*R*)[21] |
| | **1b** | 93 | 57 | | **2b** | 83 | 20 | |
| | **1c** | 70 | 70 | | **2c** | 70 | 84 | |
| | **1d** | 90 | 30 | | **2d** | 50 | 85 | |
| | **1e** | 90 | 60 | | **2e** | 40 | 75 | |
| | **1f** | 70 | 70 | | **2f** | 90 | 50 | |
| | **1g** | 79 | 49 | | **2h** | 80 | 85 | |
|  | **1a** | 40 | 30 | (+)-(*S*)[20] | **2a** | 45 | 34 | (−)-(*R*)[20] |
| | **1b** | 55 | 50 | | **2b** | 65 | 60 | |
| | **1c** | 25 | 50 | | **2c** | 60 | 50 | |
| | **1d** | 80 | 40 | | **2d** | 50 | 40 | |
| | **1e** | 80 | 35 | | **2e** | 70 | 50 | |
| | **1f** | 50 | 30 | | **2f** | 50 | 30 | |
| | **1g** | 40 | 40 | | **2h** | 30 | 70 | |
|  | **1a** | 95 | 30 | (+)-(*S*)[22] | **2a** | 65 | 48 | (−)-(*R*)[22] |
| | **1b** | 70 | 58 | | **2b** | 50 | 60 | |
| | **1c** | 40 | 55 | | **2c** | 50 | 60 | |
| | **1d** | 70 | 40 | | **2d** | 50 | 60 | |
| | **1e** | 90 | 45 | | **2e** | 99 | 35 | |
| | **1f** | 30 | 30 | | **2f** | 75 | 50 | |
| | **1g** | 40 | 40 | | **2h** | 45 | 70 | |
|  | **1b** | 99 | 33 | (+)-(1*R*,2*S*)[23] | **2b** | 45 | 50 | (−)-(1*S*,2*R*)[23] |
| | **1c** | 60 | 30 | | **2c** | 99 | 35 | |
| | **1e** | 80 | 25 | | **2e** | 97 | 30 | |
| | **1g** | 99 | 20 | | **2h** | 99 | 30 | |

[a] Reaction time usually 12 h.
[b] Reaction time (3 h), after 12 h yield 85%, ee 80%.
[c] Reaction time (3 h), after 12 h yield 90%, ee 50%.
[d] Reaction time (1 h), after 12 h yield 85%, ee 52%.
[e] Reaction time (3 h), after 12 h yield 98%, ee 35%.
[f] Reaction time (3 h), after 12 h yield 88%, ee 30%.

(98%) to moderate (30–40%) and with the systematic inversion of the configuration as a function of C(7)/C(12) bile acid substitution. The length of the alkyl chain between the carboxylic functions of the C(7)/C(12) substituent was shown to play a minor role, since the best results were obtained with oxalic (**3b**, **4b**) and phthalic (**3g**, **4h**) derivatives. Short substituents such as formyl gave results comparable to those obtained with the hydroxyl derivatives **3a** and **4a**. The protection of the bile acid as a C(24) methyl ester does not affect the course of the epoxidation reaction. Stilbene is epoxidized by Oxone in the presence of the protected derivative **3g** in 80% yield (ee 60%, see Table 1) and with the same yield but slightly higher ee (70%) when in the presence of the unprotected derivative **4h**. On the other hand, the epoxidation of β-methyl styrene gave 40% yield (ee 70%, Table 1) and 50% yield (ee 60%) if mediated by the protected **3g** or unprotected bile acid **4h**, respectively.

The α-β, that is, axial–equatorial, stereochemistry of the C(7) and C(12) substituents of the bile acid has been extensively reported in a previous paper[11a] and the results also confirmed in this case. In particular, an axial stereochemistry in both these positions is crucial for efficient enantioselective control on the formation of either one or the opposite enantiomer (see Fig. 1 for details). Equatorial substituents at C(7), in fact, gave the same epoxy enantiomers as axial substituents at C(12).[11a] Worthy of note, 3-keto-12-substituted bile acids afforded higher enantiomeric excesses compared with 3-keto-7-substituted homologues.

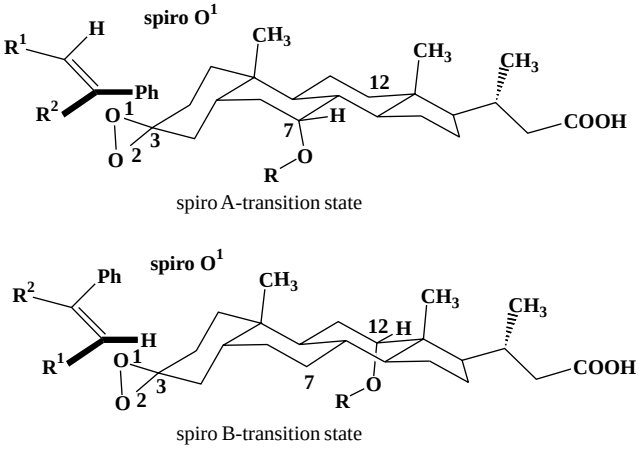



**Figure 1.** Spiro A-transition state for C(7)-substituted bile acids, spiro B-transition state for C(12)-substituted bile acids.

Ketones **3a–h** and **4a–h** demonstrated a remarkable structural durability with minor decomposition (ca. 10% in 24 h, likely by Baeyer–Villiger oxidation[11a]), under the oxidative reaction conditions. However, in some cases, we observed a decrease of the ee values as a function of the progress of the reaction. As an example, when β-methyl styrene is epoxidized with Oxone in the presence of the chiral ketone **3b** an ee value of 70% was measured after 3 h, that decreases to 50% after the period required to complete the oxidation (12 h). Attempts to minimize this parallel unselective oxidation are, at the moment, only moderately successful. The oxidation system may also be applied to the oxyfunctionalization of *cis*-alkenes.[14] Dihydronaphthalene, used as model substrate, is quantitatively oxidized to the corresponding epoxide, either to the (1*R*,2*S*) or to the (1*S*,2*R*) form, with enantiomeric excesses of 33 and 50%, respectively, depending on bile acid (Table 1, last entry).

Many studies reported that halogen substituents strongly increase the reactivity of the carbonyl group in the dioxirane mediated epoxidation. The use of fluorine substitution was first introduced into dioxirane chemistry by Curci et al.[15] in 1988 and then applied to chiral ketones for asymmetric catalysis by many research groups.[10c,16] In this frame, we have investigated 3-keto bile acid derivatives having halogen substituents near to the carbonyl function, in particular the 4-bromo derivatives **5** and **6** shown in Chart 3.[17]

Both chiral inductors are particularly active in the epoxidation reaction (yield 99% in 6 h at 0 °C), thus confirming the effect of halogen substituents on increasing of the carbonyl electrophilic reactivity.[10c] The enantiomeric excesses, however, are modest with values of 23 and 50%, respectively, using β-methyl styrene. We are currently encountering serious difficulties in the synthesis of the corresponding fluorinated bile acids.

Terminal olefins were confirmed difficult in epoxidation reactions and good enantioselectivities, ca. 70%, are obtained only after the partial conversion (50%) of the substrate. In 1999, Furstoss et al.[20] reported a detailed study on the determination of the absolute configuration of α-methyl styrene oxide and several styrene epoxide derivatives, that is, *p*-Cl, *m*-Cl, *o*-Cl, *p*-Br, *p*-$NO_2$. Conflicting optical rotation signs and, consequently, opposite absolute configurations were, in fact, described by many authors for these enantiomeric molecules. In our oxidation conditions by using 7-substituted bile acids **3a–h**, the optical rotation signs of the isolated α-methyl styrene epoxide and styrene epoxide were positive (solvent $CHCl_3$, $c=1$) and therefore assigned to a (*S*)-configuration (Table 1). The opposite (−)-*R* enantiomers were obtained for oxidations carried out in the presence of 12-substituted bile acids **4a–h**. Note that the optical rotation signs reported in our preliminary communication were not measured in chloroform.[12] Table 1 also includes the results observed with *para*-methyl styrene. A positive rotation sign was determined on the related isolated epoxide for oxidation with Oxone mediated by **3a–h** (solvent $CHCl_3$, $c=1$), however; no association with an absolute configuration might be found in the literature. The *para*-methyl styrene oxide and the styrene oxide have an identical chromatographic elution order in GC, on the chiral column used for these analysis, being the second peak the most abundant. On the other hand, based on the oxidation mechanism discussed below and depicted in Figure 1, the two alkenes should approach the dioxirane in a similar way. Following these considerations but keeping well in mind the cautions in the use of similar arguments[20] we tentatively attribute to *para*-methyl styrene oxide a (+)-*S* absolute configuration.

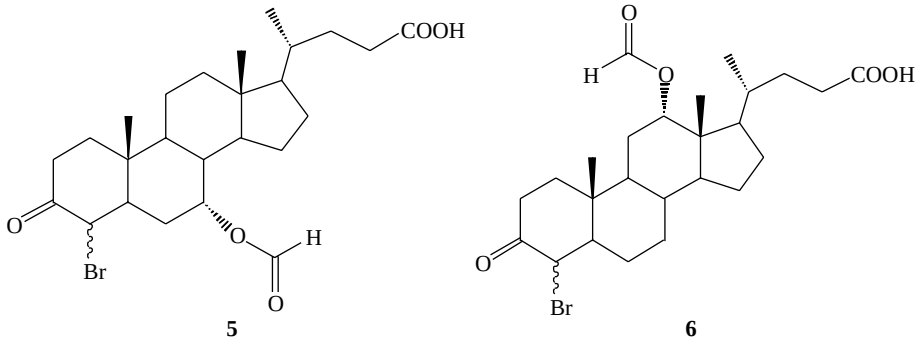
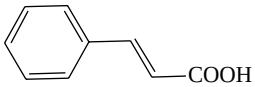
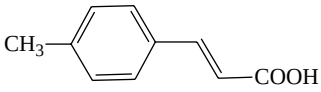
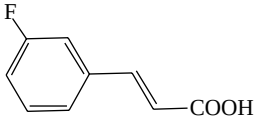
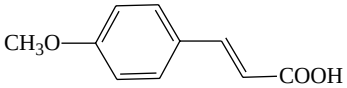
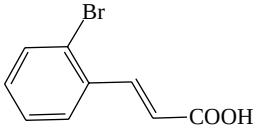



**Chart 3.** 3-Keto-4-bromo-5-β-cholan-24-oic acids, β predominant isomer, substituted at C(7) or C(12).

**Table 2**. Epoxide absolute configuration for the oxidation of cinnamic acid derivatives with Oxone, mediated by 7-substituted and 12-substituted bile acids[11a]

| Substrate | 7-Substituted bile acids | 12-Substituted bile acids |
|---|---|---|
| | Epoxide absolute configuration | Epoxide absolute configuration |
|  | (−)-(2*R*,3*S*)[13a] | (+)-(2*S*,3*R*) |
|  | (−)-(2*R*,3*S*)[13b,d] | (+)-(2*S*,3*R*) |
|  | (−)-(2*R*,3*S*)[13b,d,e] | (+)-(2*S*,3*R*) |
|  | (−)-(2*R*,3*S*)[13e,16a] | (+)-(2*S*,3*R*) |
|  | (−)-(2*R*,3*S*)[13b,d,e] | (+)-(2*S*,3*R*) |

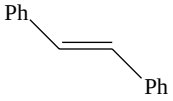
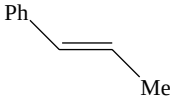
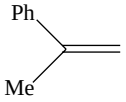
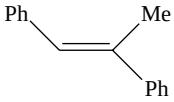
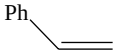
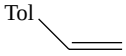
## 2.2. Mechanistic studies

In a previous paper on the epoxidation of cinnamic acid derivatives with the bile acid–Oxone system we have evaluated the minimized dioxirane–alkene adducts with the help of MM2 methods.[11a] Despite the low level of the calculations, the theoretical approach is effectively limited by such large system, evidence was provided for a preferential approach of the olefin to the lipophilic face of the bile acid, approach spiro $O^1$, with the phenyl substituent of the olefin directed toward this face. Computational studies have shown that spiro transition states are favored for the epoxidation of ethylene with dimethyldioxirane[24] and in the epoxidation of *trans*-di- and trisubstituted olefins with Oxone in the presence of fructose-derived ketones.[8a,25] On the other hand, the occurrence of an attractive interaction between π-conjugating substituents and the lipophilic face of the bile acid may parallel similar interactions proposed by Shi et al. in fructose mediated oxidations.[8a] The importance of asynchronicity in the dioxirane enantioselective epoxidation has been recently demonstrated.[26] According to the general view tending to rationalize the stereochemical course of this epoxidation in terms of a spiro model, the stereochemical outcome of the reaction for cinnamic acids, that is, $R^1$=COOH and $R^2$=H, should give rise, on the basis of the absolute configuration of the resulting epoxides collected in Table 2, to a spiro A-transition state when the bile acid is C(7) substituted, or a spiro B-transition state, when C(12) substituted (Fig. 1).

The absolute configuration of the resulting cinnamic acid epoxides is based on literature data[13] and recent VCD calculations.[13b,d] We have now applied the mechanistic approach shown in Figure 1 to the epoxidation of the unfunctionalized alkenes of this study, all containing at least a phenyl ring. The spiro A-transition state, related to a C(7) substitution of the bile acids, fully accounts for the stereochemical outcome of the reaction, as shown in Table 3.

The switch to a spiro B-transition state, proposed for C(12) substituted bile acids, gives rise to the opposite enantiomeric epoxides. From these considerations we may assert that at least for cinnamic acid-like and unfunctionalized alkenes, all containing a phenyl ring in the molecular framework, the proposed spiro model well predicts the experimental findings. We would like to point out, however, that, at this stage and taking into account the low level of

**Table 3**. Expected absolute configuration, based on the proposed spiro transition state model of Figure 1, and experimentally found absolute configuration for the epoxidation of the unfunctionalized alkenes of this study with 3-keto-7-substituted bile acids

| Substrate | Expected absolute configuration | Found absolute configuration |
|---|---|---|
|  | (*S*,*S*) | (−)-(*S*,*S*)[18] |
|  | (*S*,*S*) | (−)-(*S*,*S*)[19] |
|  | (*S*) | (+)-(*S*)[20] |
|  | (*S*,*S*) | (−)-(*S*,*S*)[21] |
|  | (*S*) | (+)-(*S*)[20] |
|  | (*S*) | (+)-(*S*)[22] |

calculations, the alternative spiro $O^2$ approach cannot be completely excluded. Work is in progress on this important problem.

## 3. Conclusions

In summary, we have demonstrated that the use of bile acid inducers having a carbonyl function at carbon C(3) and suitable axial C(7) or C(12) substituents has a fundamental effect on the reactivity and selectivity in asymmetric epoxidations with Oxone. The two-way enantioselective control of the stereochemistry of the resulting epoxide is strictly regulated by the bile acid inductor as a function of substitutions at carbons C(7) or C(12). Also in this case, the spiro transition state model may be successfully applied to predict the stereochemical outcome of the reaction.

## 4. Experimental

### 4.1. General methods

Oxidation reactions were monitored by quantitative GC analysis using a Megadex DETTBSβ capillary column. Optical rotations were measured in $CHCl_3$. Oxone and the alkenes of this study are all commercially available products used as received.

### 4.2. General procedure for epoxidation reactions

In a 10 mL volumetric flask the alkene (0.085 mmol) and the chiral ketone **3a**–**h** or **4a**–**h** (0.085 mmol) were dissolved in 2 mL of $CH_3CN$ and mixed with 2 mL of an aqueous solution of 5% $NaHCO_3$, pH ca. 8. After cooling to 0 °C, 0.255 mmol of Oxone and 0.85 mmol of $NaHCO_3$ dissolved in 1 mL of water containing $4\times10^{-4}$ M EDTA were added under stirring. After 1 h reaction time a second portion of the solution containing the oxidant was added to the reaction mixture. Samples of the mixture were taken out at fixed times of 1, 3, 12 h, respectively, extracted with ethyl acetate and submitted to GC analysis on the chiral column to estimate both the alkene conversion and the enantiomeric excess. For the epoxidations carried out on preparative scale, the reaction mixtures were treated as described above and the epoxides were separated from the crude mix by column chromatography over silica gel, characterized by $^1H$ and $^{13}C$ NMR analysis and submitted to optical rotation measurement. The absolute configuration were obtained by comparison with literature values, see text for details.

**4.2.1. 3-Keto-7α-hydroxy- and 3-keto-12α-hydroxy-5β-cholan-24-oic acid (3a, 4a).** Three grams (7.6 mmol) of commercially available chenodeoxycholic or deoxycholic acid are dissolved in MeOH (30 mL) and reacted with 1 mL of concentrated $H_2SO_4$. The solution is refluxed for 1 h, concentrated and treated with aqueous saturated $NaHCO_3$ (30 mL). The reaction mixture is extracted with ethyl acetate and dried over anhydrous $Na_2SO_4$. The solvent was removed in vacuum to give the crude methyl ester in almost quantitative yield. The further oxidation of the C(3) hydroxy function was carried out via oxidation with the Oppenauer's reagent[27] according to the following simple and straightforward procedures. The appropriate ester and aluminium *tert*-butoxide (3.6 g, 14.6 mmol) in a mixture of dry benzene (90 mL) and dry acetone (40 mL) were boiled under reflux for 18 h. The turbid reaction product was cooled and poured with stirring into 2 N sulphuric acid (60 mL). The benzene layer was separated and washed (twice) with water, aqueous sodium hydrogen carbonate and water. After drying ($Na_2SO_4$), the solvent was removed under reduced pressure to give the expected carbonyl derivative. The foregoing precursor was hydrolyzed by boiling it for 4 h under reflux with 20 mL of 10% NaOH in methyl alcohol (40 mL). The solution was then diluted with water (70 mL) and concentrated under reduced pressure to remove methyl alcohol. After cooling the solution was acidified with HCl 5%. Crystalline product was filtered off in nearly 50% yield. Compound **3a**: White crystals; mp 111–114 °C (lit.[28] 113–115 °C); $[\alpha]_D^{20}$ +13.5 (*c* 1.7, $CHCl_3$); selected $^1H$ NMR[28,29] resonances (300 MHz, $CD_3OD$): δ 0.69 (s, 3H, C*H*$_3$-18), 1.01 (d, $J=6.2$ Hz, 3H, C*H*$_3$-21), 1.07 (s, 3H, C*H*$_3$-19), 3.52 (dd, $J=J'=14.6$ Hz, 1H, *H*-4axial), 3.90 (br s, 1H, *H*-7β). Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.35; H, 9.80. Compound **4a**: white crystals; mp 154–156 °C (lit.[28] 155–157 °C); $[\alpha]_D^{20}$ +44.1 (*c* 1.6, $CHCl_3$); selected $^1H$ NMR[28,29] resonances (300 MHz, $CD_3OD$): δ 0.69 (s, 3H, C*H*$_3$-18), 1.05 (d, $J=$ 5.7 Hz, 3H, C*H*$_3$-21), 1.08 (s, 3H, C*H*$_3$-19), 2.87 (dd, $J=J'=14.0$ Hz, 1H, *H*-11axial), 4.05 (br s, 1H, *H*-12β). Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.47; H, 9.50.

**4.2.2. 3-Keto-7α-succinyloxy-5β-cholan-24-oic acid (3d).**[11a] Five grams of chenodeoxycholic acid were suspended in ethyl acetate (30 mL) in the presence of succinic anhydride (6 g, 60 mmol), triethylamine (1.27 mL, 12.7 mmol) and DMAP (0.15 g, 1.27 mmol). The reaction mixture, monitored by TLC, was refluxed for 40 h. Ethyl acetate (20 mL) and 15 mL of water were then added to the

mixture. The organic layer was washed with acid water pH ca.1, dried over anhydrous $Na_2SO_4$ and evaporated to obtain the bis-hemisuccinate. The identity of the intermediate could be validated by $^1$H NMR (300 MHz, $CDCl_3$/$CD_3OD$ 1:1 v/v): $\delta$ 0.69 (s, 3H, C$H_3$-18), 0.87 (s, 3H, C$H_3$-19), 0.87 (d, $J$=6.5 Hz, 3H, C$H_3$-21), 4.55 (m, 1H, $H$-3β), 4.82 (br s, 1H, $H$-7β). The C(3) hydrolysis of the product was obtained by dissolving the it in MeOH–NaOH 5% (1/1 v/v) After 1 h the solution is acidified with dilute $H_2SO_4$. Addition of 50 mL of $H_2O$ caused the precipitation of the 3α-hydroxy-7α-hemisuccinate derivative that was recovered by filtration. The further oxidation of the C(3) hydroxy function was carried out via oxidation with the Jones' reagent.[30] This reagent is obtained by adding 2.2 g of chromium trioxide to 2.8 mL of concentrated sulfuric acid and the solution diluted to 10 mL with water. Thus, the hydoxy bile acid precursor was dissolved in 100 mL of acetone and treated with Jones' reagent until a slight permanent orange color was obtained. After standing for 5 min, several drops of isopropyl alcohol were added to destroy the oxidant in excess. The reaction mixture was filtrated over Celite, concentrated under reduced pressure, diluted with 20 mL of water and extracted with ethyl acetate. The organic layer was dried over anhydrous $Na_2SO_4$ and the solvent was removed in vacuum to give 3.5 g (70% overall yield) of the expected carbonyl derivative. Compound **3d**: mp 120–125 °C (dec) (hexane–EtOAc); $[\alpha]_D^{20}$ +17.3 (*c* 1.5, $CHCl_3$); selected $^1$H NMR resonances (300 MHz, $CDCl_3$): $\delta$ 0.70 (s, 3H, C$H_3$-18), 0.95 (d, $J$=6.5 Hz, 3H, C$H_3$-21), 1.04 (s, 3H, C$H_3$-19), 2.98 (dd, $J=J'$=14.6 Hz, 1H, $H$-4axial), 5.05 (br s, 1H, $H$-7β). Calcd for $C_{28}H_{42}O_7$: C, 68.54; H, 8.63. Found: C, 68.16; H, 9.01.

**4.2.3. 3-Keto-7α-oxalyloxy- (3b), 3-keto-12α-oxalyloxy- (4b), 3-keto-12α-succinyloxy- (4d), 3-keto-7α-glutaryloxy- (3e), 3-keto-12α-glutaryloxy- (4e), 3-keto-7α-adipoyloxy- (3f), 3-keto-12α-adipoyloxy-5β-cholan-24-oic methyl ester (4f).** One gram (2.5 mmol) of **3a**- or **4a**-methyl esters were dissolved in 10 mL of $CH_2Cl_2$ containing TEA (2.5 mmol) and slowly added, under stirring, to a solution of the appropriate dichloride derivative, that is, oxalyl, succinyl, glutaryl or adipoyl dichloride, 7.5 mmol dissolved in 5 mL of $CH_2Cl_2$. After 12 h at room temperature the reaction mixture was treated with 10 mL of acid water (HCl 5%) and left under stirring for 4 h. The organic layer was separated, dried on anhydrous $Na_2SO_4$, concentrated and the expected derivatives purified by column chromatography (petroleum ether/ethyl acetate/acetic acid 60:40:1). Compound **3b**: syrup, 85% yield; $[\alpha]_D^{20}$ −16.2 (*c* 5.0, $CHCl_3$); selected $^1$H NMR resonances (300 MHz, $CDCl_3$): $\delta$ 0.70 (s, 3H, C$H_3$-18), 0.93 (d, $J$=6.8 Hz, 3H, C$H_3$-21), 1.07 (s, 3H C$H_3$-19), 3.20 (dd, $J=J'$=14.6 Hz, 1H, $H$-4axial), 3.62 (s, 3H, $OCH_3$), 5.17 (br s, 1H, $H$-7β). Calcd for $C_{28}H_{40}O_7$: C, 68.83; H, 8.25. Found: C, 68.36; H, 8.30. Compound **4b**: syrup, 83% yield; $[\alpha]_D^{20}$ +74.4 (3.4, $CHCl_3$); selected $^1$H NMR resonances (300 MHz, $CDCl_3$): $\delta$ 0.80 (s, 3H, C$H_3$-18), 0.82 (d, $J$=6.2 Hz, 3H, C$H_3$-21), 1.12 (s, 3H, C$H_3$-19), 2.72 (dd, $J=J'$=14.0 Hz, 1H, $H$-11axial), 3.63 (s, 3H, OC$H_3$), 5.32 (br s, 1H, $H$-12β). Calcd for $C_{28}H_{40}O_7$: C, 68.83; H, 8.25. Found: C, 68.45; H, 8.09. Compound **4d**: 76% yield, mp 138–141 °C (hexane–EtOAc); $[\alpha]_D^{20}$ +66.4 (*c* 2.5, $CHCl_3$); selected $^1$H NMR resonances (300 MHz, $CDCl_3$): $\delta$ 0.78 (s, 3H, C$H_3$-18), 0.81 (d, $J$=6.1 Hz, 3H, C$H_3$-21), 1.00 (s, 3H, C$H_3$-19), 2.62 (m, 5H, $H$-11axial, $(COCH_2)_2$), 3.67 (s, 3H, OC$H_3$), 5.15 (br s, 1H, $H$-12β). Calcd for $C_{29}H_{44}O_7$: C, 69.02; H, 8.79. Found: C, 68.76; H, 9.11. Compound **1e**: syrup, 72% yield; $[\alpha]_D^{20}$ +4.2 (*c* 3.5, $CHCl_3$); selected $^1$H NMR resonances (300 MHz, $CDCl_3$): $\delta$ 0.70 (s, 3H, C$H_3$-18), 0.94 (d, $J$=6.0 Hz, 3H, C$H_3$-21), 1.02 (s, 3H, C$H_3$-19), 2.98 (dd, $J=J'$=14.6 Hz, 1H, $H$-4axial), 3.64 (s, 3H, OC$H_3$), 5.01 (br s, 1H, 1H, $H$-7β). Calcd for $C_{31}H_{46}O_7$: C, 70.16; H, 8.74. Found: C, 71.00; H, 8.88. Compound **4e**: syrup, 74% yield; $[\alpha]_D^{20}$ +57.5 (*c* 1.2, $CHCl_3$); selected $^1$H NMR resonances (300 MHz, $CDCl_3$): $\delta$ 0.75 (s, 3H, C$H_3$-18), 0.80 (d, $J$=5.8 Hz, 3H, C$H_3$-21), 0.99 (s, 3H, C$H_3$-19), 2.68 (dd, $J=J'$=14.0 Hz, 1H, $H$-11axial), 3.62 (s, 3H, OC$H_3$), 5.12 (br s, 1H, $H$-12β). Calcd for $C_{31}H_{46}O_7$: C, 70.16; H, 8.74. Found: C, 71.02; H, 8.18. Compound **3f**: syrup, 37% yield; $[\alpha]_D^{20}$ +5.6 (*c* 1.3, $CHCl_3$); selected $^1$H NMR resonances (300 MHz, $CDCl_3$): $\delta$ 0.71 (s, 3H, C$H_3$-18), 0.96 (d, $J$=6.2 Hz, 3H, C$H_3$-21), 1.05 (s, 3H, C$H_3$-19), 3.00 (dd, $J=J'$=14.6 Hz, 1H, $H$-4axial), 3.64 (s, 3H, OC$H_3$), 5.01 (br s, 1H, $H$-7β). Calcd for $C_{32}H_{48}O_7$: C, 70.56; H, 8.88. Found: C, 70.12; H, 8.47. Compound **4f**: syrup, 40% yield; $[\alpha]_D^{20}$ +61.2 (*c* 2.5, $CHCl_3$); selected $^1$H NMR resonances (300 MHz, $CDCl_3$): $\delta$ 0.78 (s, 3H, C$H_3$-18), 0.80 (d, $J$=6.1 Hz, 3H, C$H_3$-21), 1.01 (s, 3H, C$H_3$-19), 2.70 (dd, $J=J'$=14.0 Hz, 1H, $H$-11axial), 3.66 (s, 3H, OC$H_3$), 5.15 (br s, 1H, $H$-12β). Calcd for $C_{32}H_{48}O_7$: C, 70.56; H, 8.88. Found: C, 70.21; H, 8.74.

**4.2.4. 3-Keto-7α-malonyloxy- (3c), 3-keto-12α-malonyloxy-5β-cholan-24-oic methyl ester (4c).** One gram (2.5 mmol) of **3a**- or **4a**-methyl esters dissolved in anhydrous toluene (30 mL) were added to a solution containing 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid, 2.75 mmol). The reaction mixture was kept under reflux for 4 h, cooled and concentrated under reduced pressure affording the malonyl derivatives in almost quantitative yield. Compound **3c**: sticky oil; $[\alpha]_D^{20}$ −1.8 (*c* 2.0, $CHCl_3$); selected $^1$H NMR resonances (300 MHz, $CDCl_3$): $\delta$ 0.68 (s, 3H, C$H_3$-18), 0.95 (d, $J$=6.2 Hz, 3H, C$H_3$-21), 1.02 (s, 3H, C$H_3$-19), 2.91 (dd, $J=J'$=14.6 Hz, 1H, $H$-4axial), 3.42 (m, 2H, $COCH_2CO$), 3.64 (s, 3H, OC$H_3$), 5.03 (br s, 1H, $H$-7β). Calcd for $C_{29}H_{42}O_7$: C, 69.29; H, 8.42. Found: C, 68.86; H, 8.55. Compound **4c**: mp 143–145 °C, (hexane–EtOAc); $[\alpha]_D^{20}$ +73.1 (*c* 1.3, $CHCl_3$); selected $^1$H NMR resonances (300 MHz, $CDCl_3$): $\delta$ 0.78 (s, 3H, C$H_3$-18), 0.83 (d, $J$=6.4 Hz, 3H, C$H_3$-21), 1.02 (s, 3H, C$H_3$-19), 2.70 (dd, $J=J'$=14.0 Hz, 1H, $H$-11axial), 3.42 (m, 2H, $COCH_2CO$), 3.68 (s, 3H, OC$H_3$), 5.21 (br s, 1H, $H$-12β). Calcd for $C_{29}H_{42}O_7$: C, 69.29; H, 8.42. Found: C, 68.16; H, 8.57.

**4.2.5. 3-Keto-7α-phtaloyloxy- (3g), 3-keto-12α-phtaloyloxy-5β-cholan-24-oic methyl ester (4g).** To a toluene solution (40 mL) containing **3a**- or **4a**-methyl esters (1 g, 2.5 mmol), phtalic anidride (3.75 mmol) and imidazole (2.5 mmol) were added under stirring. The mixture was refluxed for 40 h, monitoring the progress of the reaction by TLC (petroleum ether/ethyl acetate 4:1). After completion the mixture was washed with acid water (15 mL, HCl 5%) and extracted with ethyl acetate. The organic layer was separated, dried on anhydrous $Na_2SO_4$, concentrated and the expected derivatives purified by column chromatography

(petroleum ether/ethyl acetate/acetic acid 80:20:1). Yields 83 and 87%, respectively. Compound **3g**: mp 105–110 °C (dec), (hexane–EtOAc); $[\alpha]_D^{20}$ −15.1 (*c* 1.1, $CHCl_3$); selected $^1$H NMR resonances (300 MHz, $CDCl_3$): $\delta$ 0.72 (s, 3H, C$H_3$-18), 0.95 (d, $J$=6.0 Hz, 3H, C$H_3$-21), 1.08 (s, 3H, C$H_3$-19), 2.92 (dd, $J=J'$=14.6 Hz, 1H, *H*-4axial), 3.68 (s, 3H, OC$H_3$), 5.35 (br s, 1H, *H*-7β), 7.44 (d, $J$=7.2 Hz, 1H, Ar-*H*), 7.60 (m, 2H, Ar-*H*), 7.98 (d, $J$=7.0 Hz, 1H, Ar-*H*). Calcd for $C_{33}H_{44}O_7$: C, 71.71; H, 8.02. Found: C, 71.24; H, 7.89. Compound **4g**: the $^1$H NMR spectrum is almost identical to that of **4h** except for the methyl ester resonance $\delta$ 3.65 (s, 3H, OC$H_3$).

**4.2.6. 3-Keto-12α-phtaloyloxy-5β-cholan-24-oic acid (4h).** The free bile acid **4h** was obtained from **4g** upon reaction with KOH 5% (20 mL) under reflux for 1 h. The reaction mixture was treated with concentrated HCl and extracted with ethyl acetate. The organic layer, separated, dried and concentrated afforded the expected product in almost quantitative yield. Compound **4h**: mp 92–98 °C (dec), (hexane–EtOAc); $[\alpha]_D^{20}$ +46.7 (*c* 1.4, $CHCl_3$); selected $^1$H NMR resonances (300 MHz, $CDCl_3$): $\delta$ 0.86 (s, 3H, C$H_3$-18), 0.98 (d, $J$=6.2 Hz, 3H, C$H_3$-21), 1.05 (s, 3H, C$H_3$-19), 2.72 (dd, $J=J'$=14.0 Hz, 1H, *H*-11axial), 5.44 (br s, 1H, *H*-12β), 7.60 (m, 3H, Ar-*H*), 7.90 (d, $J$=7.1 Hz, 1H, Ar-*H*). Calcd for $C_{32}H_{42}O_7$: C, 71.35; H, 7.86. Found: C, 72.02; H, 8.20.

**4.2.7. 3-Keto-4β-bromo-7α-formyloxy-5β-cholan-24-oic acid (5).** This derivative was prepared from the corresponding 3-keto-7α-formyloxy-5β-cholan-24-oic acid by treatment with bromine in DMF, according with literature procedures;[17,31] diasteromeric $\alpha/\beta$ ratio 1:9, mp 164–166 °C (hexane–EtOAc); selected $^1$H NMR resonances (300 MHz, $CDCl_3$): $\delta$ 0.70 (s, 3H, C$H_3$-18), 0.94 (d, $J$=5.4 Hz, 3H, C$H_3$-21), 1.10 (s, 3H, C$H_3$-19), 5.15 (m, 1H, *H*-7), 5.33 (d, $J$=11.7 Hz, 1H, *H*-4), 8.08 (s, 1H, 7-CHO).

**4.2.8. 3-Keto-4β-bromo-12α-formyloxy-5β-cholan-24-oic acid (6).** This derivative was prepared from the corresponding 3-keto-12α-formyloxy-5β-cholan-24-oic acid by treatment with bromine in DMF, according with literature procedures[17,31]; diasteromeric $\alpha/\beta$ ratio ca. 1:9, mp 183–184 °C (hexane–$Et_2O$); selected $^1$H NMR resonances (300 MHz, $CDCl_3$): $\delta$ 0.80 (s, 3H, C$H_3$-18), 0.84 (d, $J$=6.3 Hz, 3H, C$H_3$-21), 1.07 (s, 3H, C$H_3$-19), 4.95 (d, $J$=11.7 Hz, 1H, *H*-4), 5.29 (m, 1H, *H*-12), 8.11 (s, 1H, 12-CHO).

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.052.

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