Published in Chirality 10, issue 9, 804-807, 1998
which should be used for any reference to this work

Influence of the Nature and Substitution of Chiral 2,3-Epoxy Alcohol Derivatives on the Enantiomeric Elution Order on Chiralcel OD Column

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ABSTRACT A number of 2,3-epoxy alcohol derivatives **(1–16),** obtained either as racemates or through the Sharpless asymmetric epoxidation reaction, were studied on a Chiralcel OD column. Nearly all compounds exhibit good enantioselective resolution on this chiral support. The order of elution of enantiomers is reversed between nerol and geraniol compounds. For 2,3-epoxy alcohols bearing a remote alkoxy (or silyloxy) group, the order of the enantiomeric elution alternates with the number n (n = 1–3) of methylenic groups present between the epoxide ring and the terminal OR (R = p – BrBn or $OSitBuPh_2$) functionality. In the case of *trans* 2,3-epoxy alcohols for the same number n, the order of elution is reversed when changing the terminal group –OSi to –OR. The latter group greatly improves the separation of the two enantiomers.

KEY WORDS: 2,3-epoxyalcohols; enantiomeric elution order; protective groups; chain length influence

For the last decade, intense interest has focused on the development of synthetic methods leading to optically active synthons possessing a 1,2, 1,3, 1,2,3 polyhydroxylated frame.[1–3] The Sharpless asymmetric epoxidation reaction (SAE)[4] has found an enormous application for these synthons[5,6] since its discovery in 1980. The homochiral 2,3-epoxyalcohols synthesized from the corresponding allylic alcohols through the SAE reaction usually possess high enantiomeric purity. The determination of their enantiomeric excess necessitates accurate analytical methods. High performance liquid chromatography and commercially available chiral stationary phases (CSP) contribute greatly in resolving these problems.[7,8] Among the cellulose CSP, the Chiralcel OD cellulose tris[3,5-dimethylphenylcarbamate] stationary phase has been widely used for chiral separation of many compounds.[9]

The aim of this paper is to study the enantiomeric resolution of a number of 2,3-epoxy alcohol derivatives (Fig. 1) and to discuss how the enantiomeric elution order is influenced by the type of epoxy alcohol, the absolute configuration of the asymmetric centers, and the protective groups on the hydroxyl function. The influence of the type of epoxy alcohol, of the substituents on the hydroxy group and of the absolute configuration on the enantiomeric elution order will be discussed.

MATERIALS AND METHODS

Instrumentation

Thin layer chromatography was performed using ALUGRAM SIL G/UV_{254} foils (20 × 20 cm; Macherey-Nagel, Strasbourg, France). Medium pressure liquid chromatography was carried out on a Jobin-Yvon Moduloprep (Longjumeau, France) apparatus equipped with a UV or refractometric detector, using Merck (Darmstadt, Germany) silica 15 µm or Amicon (Beverly, MA) silica 6–35 µm (L = 15 cm, ϕ = 0.20 cm.) Analytical liquid chromatography used a Kratos (Ramsey, NJ) Spectroflow 400 pump, a UV 759A detector, and a Rheodyne (Cotati, CA) injector (20 µl). The columns used were either Waters (Rochester, MN) Novapack silica (L = 15 cm, ϕ = 0.39 cm) for chemical purity determination or a Chiralcel OD (L = 25 cm, ϕ = 0.46 cm) (Daicel Chemical Industries Ltd., Düsseldorf, Germany), for determination of enantiomeric excess (% ee). Purity of non-UV absorbing compounds was determined by gas capillary chromatography with a Hewlett-Packard (Corvallis, OR) G.C. apparatus (T oven = 190°C, T inj. = 230°C, T det. = 220°C) on an SE30 column (L = 10 m, ϕ = 0.53). Infrared spectra were recorded on a Perkin-Elmer (Oak Brook, IL) 883 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded using a Bruker (Wissenbourg, France) (AC250 instrument with TMS as internal reference). Optical rotations were measured on a Perkin-Elmer 141 polarimeter.

Chemical and Methods

Commercially available reagents were used as supplied. All solvents were distilled prior to use. The general proce-

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Received for publication 8 October 1997; Accepted 5 January 1998

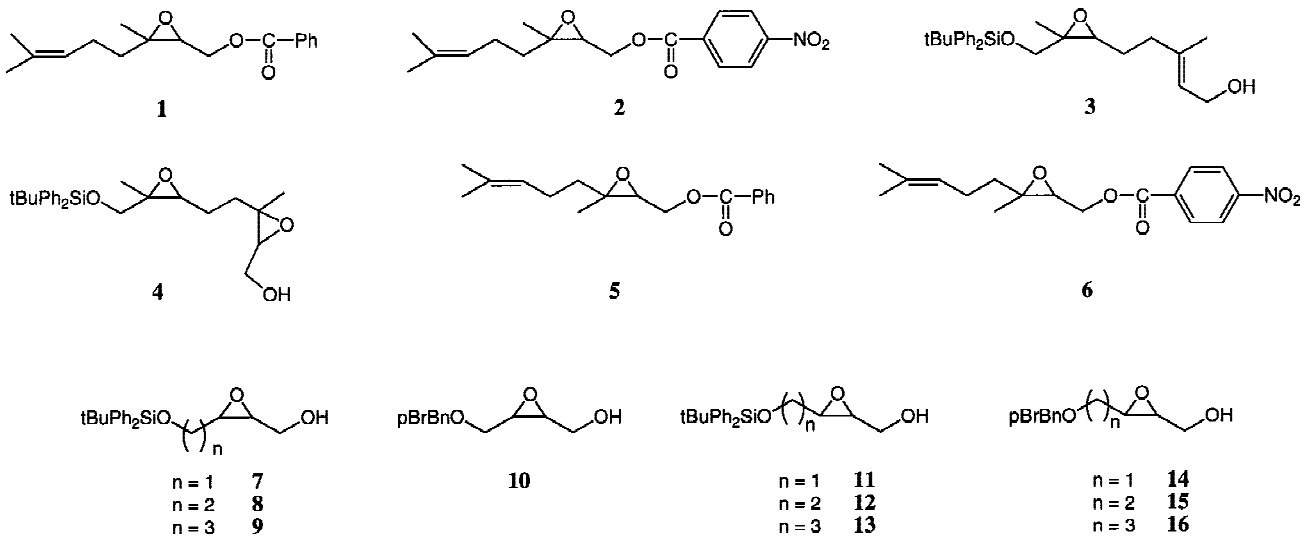

Fig. 1. Structures of the racemic epoxides studied.

dure for synthesis of racemic α,β-epoxy alcohols was as follows: A mixture of allylic alcohol (1.5 mmol/10 ml), m-chloroperbenzoic acid (3 mmol/10 ml) and sodium bicarbonate (4 mmol/10 ml) in anhydrous methylene chloride was stirred for 17 hr at room temperature. The reaction was quenched by addition of an 10% aqueous solution of sodium hydrogensulfite (1 ml/mmol) and stirred at 0°C for an additional 30 min. Organic phase was washed with water, saturated NaCl and three times with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. The epoxy alcohol was purified by medium pressure liquid chromatography.

The general procedure for the Sharpless epoxidation reaction for these compounds was that described previously.[10,11]

Among all the epoxides synthesized in our laboratorym,[10,12] we give spectroscopic data only for those that have not been reported previously.

(2S,3S) and (2R,3R)-1-(benzoyloxy)-3,7-(dimethyl)-2,3-epoxyoct-6-ene (5). To a solution of epoxygeraniol (200 mg, 1.18 mmol) in methylene chloride (9 ml) was added under stirring and N_2, pyridine (0.19 ml, 2.36 mmol) followed by benzoyl chloride (0.47 ml, 3.5 mmol). The reaction mixture was stirred for 3 hr at room temperature and then quenched with sat. aqueous $NaHCO_3$ (3 ml/mmol) and extracted three times with ether (10 ml). The organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel column chromatography (eluent petroleum ether/ether 80/20) leading to 295 mg (91% yield) of compound **5.** Rf = 0.31. IR (film), ν cm^{-1}: 2970-2929 (C-H), 1723 (C = O), 1107 (C-O). ^1H NMR: (250 MHz, $CDCl_3$), δ ppm, 8.09–7.54–7.44 (m, 5H, Ar), 5.09 (t hept, 1H, $J_{H6\text{-}H5}$ = 7 Hz, $J_{H6\text{-}H8,9}$ = 1.5 Hz, H_6), 4.56 (dd, 1H, $J_{H1A\text{-}H1B}$ = 12.2 Hz, $J_{H1A\text{-}H2}$ = 4.5 Hz, H_{1A}), 4.29 (dd, 1H, $J_{H1A\text{-}H1B}$ = 12,2 Hz, $J_{H1B\text{-}H2}$ = 6.7 Hz, H_{1B}), 3.14 (dd, 1H, $J_{H2\text{-}H1B}$ = 6.7 Hz, $J_{H2\text{-}H1A}$ = 4.5 Hz, H_2), 2.10 (q large, 2H, J = 7.5 Hz, H_5), 1.69–1.58 (m, 2H, H_4), 1.66-1.60 (2d, 6H, J = 1.5; 1.5 Hz, H_8-H_9), 1.38 (s, 3H, H_{10}). ^{13}C NMR: (63 MHz, $CDCl_3$), δ ppm, 166.4 (C_{11}), 133.2–129.8–128.4 (CH Ar), 132.3 (C_7), 123.2 (C_6), 64.0 (C_1), 60.7 (C_3), 59.8 (C_2), 38.3 (C_5), 25.7–17.7 (C_8-C_9), 23.7 (C_4), 17.0 (C_{10}). Analysis calculated for $C_{17}H_{22}O_3$: C 74.42, H 8.08. Found C 74.78, H 8.18.

(2S,3R) and (2R,3S)-5-(tert-butyldiphenylsilyloxy)-2,3-epoxypentan-1-ol (8). This was purified by silica gel column chromatography using a mixture of petroleum ether and ether (60/40) as eluent. Starting from 12.25 g (36.03 mmol) of allylic alcohol we obtained 11.28 g of epoxy alcohol **8** (88% yield). Rf = 0.11. IR (film), ν cm^{-1}: 3436 (O-H), 2936–2864 (C-H), 1101 (C-O). ^1H NMR: (250 MHz, $CDCl_3$), δ ppm, 7.67–7.40 (m, 10H, Are), 3.79 (m, 2H, H_5), 3.74 (m, H_1), 3.21 (m, 2H, H_2–H_3), 2.27 (m, 1H, OH), 1.86 (m, 2H, H_4), 1.07 (s, 9H, tBu). ^{13}C NMR: (63 MHz, $CDCl_3$), δ ppm, 135.57–129.87–127.81 (CH Ar), 133.17 (C_q Ar), 61.37–60.83 (C_5-C_1), 56.28–54.91 (C_2-C_3), 30.80 (C_4), 26.86 ($C(CH_3)_3$), 19.14 ($C(CH_3)_3$). Analysis calculated for $C_{21}H_{28}SiO_3$: C 70.74, H 7.92. Found C 70.91, H 8.16. The SAE reaction was performed with (+)diethyl tartrate (82% yield). $[\alpha]_D^{25}$ = +2.7° (c = 2.7, $CHCl_3$), %ee = 86%.

(2R,3R) and (2S,3S)-5-(p-bromobenzyloxy)-2,3-epoxypentan-1-ol (15). This was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (40/60) as eluent. Starting from 4.6 g (16.97 mmol) of allylic alcohol we obtained 4.03 g of epoxyalcohol **15** (83% yield). Rf = 0.24. IR (film), ν cm^{-1}: 3426 (O-H), 2923–2866 (C-H), 1099 (C-O). ^1H NMR: (250 MHz, $CDCl_3$), δ ppm, 7.46 (d, 2H, J = 5.9 Hz, Ar), 7.19 (d, 2H, J = 8.56 Hz, Ar), 4.46 (s, 2H, pBrPhCH_2O), 3.86 (ddd, 1H, $J_{H1A\text{-}H1B}$ = 12.5 Hz, $J_{H1A\text{-}OH}$ = 5.5 Hz, $J_{H1A\text{-}H2}$ = 2.3 Hz, H_{1A}), 3.59 (m, 3H, H_5 et H_{1B}), 3.09 (ddd, 1H, $J_{H3\text{-}H4}$ = 6.5 Hz, $J_{H3\text{-}H4}$ = 4.5 Hz, $J_{H3\text{-}H2}$ = 2.3 Hz, H_3), 2.96 (ddd, 1H, $J_{H2\text{-}H1}$ = 4.5 Hz, $J_{H2\text{-}H1}$ = 2.3 Hz, $J_{H2\text{-}H3}$ = 2.3 Hz, H_2), 2.08 (1H, $J_{H1\text{-}OH}$ = 5.5 Hz, OH), 1.83 (m, 2H, $J_{H5\text{-}H4}$ = 6.5 Hz,

TABLE 1. Capacity (k′) and separation (α) factors on Chiralcel OD column for epoxides related to nerol and geraniol*

Epoxide	k'_1	k'_2	α
1	0.71 (+)	0.90 (–)	1.27
2	2.29 (+)	3.31 (–)	1.44
3	0.80 (+)	1.07 (–)	1.24
4	1.46 (+)	2.23 (–)	1.53
5	0.74 (–)	1.34 (+)	1.80
6	6.86 (–)	7.28 (+)	1.06

*Column 25 × 0.46 cm (i.d.); eluent hexane-2-propanol (90/10); flow rate 0.5 ml/min. The sign in parentheses shows the type of chiral ligand used in order to obtain this epoxide as the major enantiomer in the SAE reaction.

$J_{H5\text{-}H4}$ = 5.5 Hz, $J_{H4\text{-}H3}$ = 4.5 Hz, H_4). ^{13}C NMR: (63 MHz, $CDCl_3$), δ ppm, 137.2–121.5 (C_q Ar), 131.5–129.2 (CH Ar), 72.3 (C_6), 67.0 (C_5), 61.7 (C_1), 58.5 (C_2), 53.6 (C_3), 32.0 (C_4). Analysis calculated for $C_{12}H_{15}BrO_3$: C 50.19, H 5.27. Found C 50.19, H 5.31. The SAE reaction was performed with (–)diethyl tartrate (85% yield). $[\alpha]_D^{25}$ = +28.4° (c = 2.7, $CHCl_3$), %ee = 78%.

(2R,3R) and (2S,3S)-6-(p-bromobenzyloxy)-2,3-epoxyhexan-1-ol (16). This was purified by silica gel column chromatography using a mixture of petroleum ether and ethyl acetate (40/60) as eluent. Starting from 6 g (21.05 mmol) of allylic alcohol we obtained 4.77 g of epoxyalcohol **16** (75% yield). Rf = 0.17. IR (film), ν cm^{-1}: 3435 (O-H), 2934–2864 (C-H), 1102 (C-O). ^{1}H NMR: (250 MHz, $CDCl_3$), δ ppm, 7.47 (d, 2H, J = 8.4 Hz, H_A $H_{A'}$, Ar), 7.20 (d, 2H, J = 8.5 Hz, $H_B H_{B'}$, Ar.), 4.44 (s, 2H, pBrPhCH_2O), 3.87 (ddd, 1H, $J_{H1A\text{-}H1B}$ = 12.5 Hz, $J_{H1A\text{-}OH}$ = 5.4 Hz, $J_{H1A\text{-}H2}$ = 2.7 Hz, H_{1A}), 3.61 (ddd, 1H, $J_{H1A\text{-}H1B}$ = 12,5 Hz, $J_{H1B\text{-}OH}$ = 7.2 Hz, $J_{H1B\text{-}H2}$ = 4.3 Hz, H_{1B}), 3.50 (m, 2H, H_6), 2.99 (m, 1H, H_3), 2.91 (ddd, 1H, $J_{H2\text{-}H1B}$ = 4.3 Hz, $J_{H2\text{-}H1A}$ = 2.7 Hz, $J_{H2\text{-}H3}$ = 2.1 Hz, H_2), 1.86 (dd, 1H, $J_{OH\text{-}H1B}$ = 7.2 Hz, $J_{OH\text{-}H1A}$ = 5.4 Hz, OH), 1.71 (m, 4H, H_4-H_5). ^{13}C NMR: (63 MHz, $CDCl_3$), δ ppm, 137.4–121.5 (C_q Ar), 131.5–129.3 5 (Ar), 72.2 (C_7), 69.8 (C_6), 61.7 (C_1), 58.5 (C_2), 55.7 (C_3), 28.5–26.2 (C_4-C_5). Analysis calculated for $C_{13}H_{17}BrO_3$: C 51.84, H 5.69. Found C 51.80, H 5.64. The SAE reaction was performed with (+)diethyl tartrate (72% yield). $[\alpha]_D^{25}$ = –21.2° (c = 2.7, $CHCl_3$), %ee = 98%.

Chromatographic Parameters

Capacity factors (k′) were calculated using the equation $k' = V_R - V_0/V_0$ where V_R is the elution volume and V_0 is the void volume. The separation factor is equal to $\alpha = k'_2/k'_1$ where k'_1 and k'_2 are the capacity factors of the two peaks.

RESULTS AND DISCUSSION

Baseline resolution was obtained for all epoxyalcohols chromatographed in this study.

Considering the epoxides issued from nerol (Table 1, **1–4**) we observe that under constant experimental conditions those that are synthesized by the SAE reaction using (+)diethyl tartrate as chiral ligand are eluted first. In all these cases, the quaternary carbon atom of the epoxide ring has (R)-absolute configuration and the two contiguous carbon chiral centers have the (R,S)-absolute configuration. It is noteworthy that the same order of elution is observed when resolving 2,3-epoxynerol by gas phase chromatography using a Rt-gDEXsa (L = 25 m, ϕ = 0.3 mm, T oven = 100 to 200°C, 2°C/min, T inj. = 220°C, T det. = 280°C) as chiral column (k'_1 = 32.26, k'_2 = 33.57, α = 1.04).

TABLE 2. Capacity (k′) and separation (α) factors on Chiralcel OD column for *cis* 2,3-epoxy alcohols*

Epoxy alcohol	k'_1	k'_2	α
7	1.25 (–)	3.00 (+)	2.40
8	1.74 (+)	2.34 (–)	1.34
9	0.76 (–)	0.92 (+)	1.20
10	2.10 (–)	2.50 (+)	1.19

*Column 25 × 0.46 cm (i.d.); eluent hexane-2-propanol (90/10) except for **10** (80/20 ratio); flow rate 0.5 ml/min. The sign in parentheses shows the type of chiral ligand used in order to obtain this epoxide as the major enantiomer in the SAE reaction.

The order of elution is reversed when examining the geraniol epoxides (Table 1, **5–6**). The first eluted compound, the major one when performing the SAE reaction with (–)diethyl tartrate, has (S)-absolute configuration on the quaternary carbon atom and (S,S)-carbon configurations of the epoxide ring.

2,3-Epoxynerol, protected by a 4-nitrobenzoate group, was resolved with a better signal separation than when using the benzoate protective group (Table 1, **1–2**). The situation is reversed with geraniol compounds where the best signal separation was obtained for the benzoate-protected epoxy alcohol. Finally the diepoxide, synthesized as previously reported,[11] showed also a better enantiomeric separation than the corresponding monoepoxide (Table 1, **3–4**).

The results concerning 2,3-epoxy alcohols bearing a remote alkoxy (or silyloxy) group are summarized in Tables 2 and 3. For *cis* 2,3-epoxyalcohols possessing a tert-butyldiphenylsilyloxy protective group **(7–9)** the order of enantiomeric elution alternated with the number of methylenic groups between the epoxide ring and the silyloxy functionality. In fact, the epoxy alcohols possessing a (2S,3R) absolute configuration on the carbon chiral centers of the epoxide ring that are the major enantiomers issued from the SAE reaction with (+)-diethyltartrate, are eluted second when n = 1 and n = 3 and first when n = 2 (Table 2). The same trend and the same order of elution for n = 1 and 2 is also observed in the case of *trans* 2,3-epoxy alcohols ((2S,3S) absolute configuration) bearing the same protective group (Table 3, compounds **11–13**).

For 2,3-*trans* epoxyalcohols, when changing the protective group (p-bromobenzyl instead of tert-butyldiphenylsilyl), we also observe an alternation in the enantiomeric elution order as a function of n. Interestingly, in this case compounds with (2S,3S) absolute configuration are eluted first when n = 1, 3, and second when n = 2 (Table 3, compounds **14–16**).

In the case of all *trans* 2,3-epoxy alcohols, changing the hydroxy protective group (from $tBuPh_2Si$ to p-BrBn) not only reverses the order of elution but also greatly improves

TABLE 3. Capacity (k′) and separation (α) factors on Chiralcel OD column for *trans* 2,3-epoxy alcohols*

Epoxy alcohol	k'_1	k'_2	α
11	1.35 (–)	1.59 (+)	1.18
12	1.19 (+)	1.59 (–)	1.34
13[a]	1.24	1.24	1.00
14	2.60 (+)	3.32 (–)	1.28
15	0.38 (–)	0.82 (+)	2.16
16	0.41 (+)	0.87 (–)	2.11

*Column 25 × 0.46 cm (i.d.); eluent hexane-2-propanol (90/10) except for **14–16** (80/20 ratio); flow rate 0.5 ml/min. The sign in parentheses shows the type of chiral ligand used in order to obtain this epoxide as the major enantiomer in the SAE reaction.
[a]Compound **13** could not be resolved under different elution conditions.

the signal separation (α values) between the two enantiomers. This is particularly interesting for *trans* 2,3-epoxy alcohols where n = 3. For these compounds there is no separation for enantiomers bearing a silyloxy protection but there is a large one (α = 2.11) when using the p-bromobenzyl group.

Chiral recognition and discrimination depend on the size and geometry of the chiral solutes, the kind of solute-CSP interactions that is dipole-dipole, hydrogen bond, hydrophobic, π-π, etc. These multiple interactions along with inclusion complexes and solvent effects contribute to the resolution for a chiral CSP of this type.

In this case, for the nerol and geraniol compounds **1–6**, it seems likely that the geometry of the quaternary chiral carbon atom of the epoxide ring plays a crucial role in the resolution process. On the other hand, for the nerol compounds **1–4**, varying the substituent of the hydroxy functionality does not affect the elution order.

For epoxy alcohols **7–9** and **11–13** possessing a $tBuPh_2Si$ protective group, the size of this group and its vicinity to the oxygen atoms that can be responsible for hydrogen bonding with the CSP might determine the preference for inclusion complex formation and thus for the elution order observed. This order might be reversed when using a less bulky group (p-BrBn) as is observed in the case of *trans* epoxyalcohols **14–16**.

CONCLUSION

In summary nearly all the epoxy alcohols studied can be conveniently separated by resolution using a Chiralcel OD column. There is a precise order of elution of the enantiomers that is function of (1) the nature of the epoxy alcohol considered (nerol-geraniol, *cis* or *trans* epoxy alcohols, number of methylenic groups present), and (2) the type of the protective group when considering the *trans* 2,3-epoxy alcohols.

The 2,3-epoxy alcohols synthesized are useful chiral synthons in our synthetic strategy for the elaboration of more complex molecules.[13–15] Their enantiomeric resolution will be also studied and published.

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