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Diastereoselective Synthesis of 7,8-Carvone Epoxides

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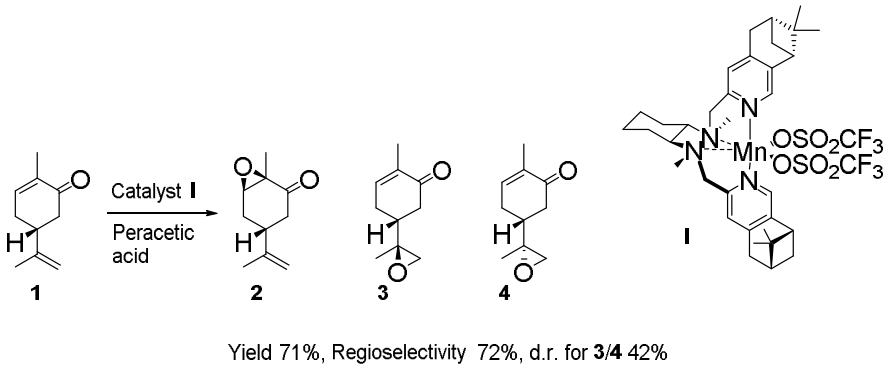
Abstract: The synthesis of the two 7,8-epoxides of carvone has been attained using organocatalysis in a two-step synthetic route through a bromoester intermediate. Among the different reaction conditions tested for the bromination reaction, moderate yields and diastereoselection are achieved using proline, quinidine, and diphenylprolinol, yielding the corresponding bromoesters that were transformed separately into their epoxides, obtaining the enantiopure products.

Keywords: organocatalysis; aminocatalysis; proline; carvone; epoxidation; epoxide

1. Introduction

Carvone is a natural product frequently used as starting material for the synthesis of other naturally occurring compounds [1]. The interest in the carvone molecule as a chiral pool starting material is based on the presence of an α,β-unsaturated carbonyl in a cyclohexane ring with a chiral centre and an extra double bond in the isopropyl chain [2–6]. Regiospecific epoxidation of carvone has been a classical challenge in organic chemistry [7]. Epoxidation of carvone in the internal double bond has been achieved in a diasteroselective reaction controlled by the chiral centre in basic conditions. However, when the epoxidation of the isopropylidene group with *m*-CPBA is carried out, no diastereoselection is obtained [8,9]. Recently, very interesting biological applications of the natural 7,8-epoxides mixture of carvone [10] have been described: of anti-inflammatory [10], antifeedant, and phytotoxic [11] nature. To obtain these epoxy derivatives, the organic oxidants used for the epoxidation reaction are rather expensive and have to be used in a stoichiometric manner, and even in those conditions, the reaction yields are rather small. For these reasons, the interest in the synthesis of the 7,8-epoxides of carvone using catalysis has increased. Many metals have been used in this catalysed oxidation reaction: gallium [12]; aluminium [12]; vanadium and tungsten [13]; and di- or tetracoordinated metals with diamines, mainly manganese [14–16] (Scheme 1) or iron [17–20], or chitosan based with manganese, copper, cobalt, or nickel [21]. In all cases, the diastereoselectivity was very small or even negligible. An alternative method used for the synthesis of the 7,8-carvone epoxides consisted of the enzymatic oxidation of carvone by cytochrome $P450_{cin}$ [22]. In the last years, there

has been a great interest in the use of greener methods for this oxidation, and it has been achieved by chemoenzymatic methods [23] or with hydrotalcites and hydrogen peroxide [24]. Another strategy has been afforded, using *N*-bromosuccinimide (NBS) in DMSO and ulterior addition of bases [25]. In all these cases, no diastereoselectivity was found (0% diastereomeric ratio, d.r.)



Scheme 1. Synthesis of the epoxides with 42 d.r.

In the last years, there has been an increasing interest in metal-free reactions, with organocatalysis being one of the most interesting areas of research in organic chemistry [26–30]. An elevated number of chiral organocatalysts has been developed, where amines play an important role and comprise the main family of organocatalysts (Figure 1).

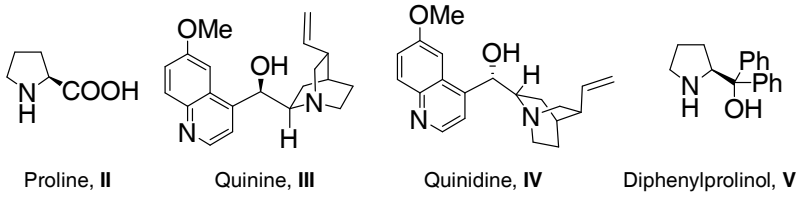


Figure 1. Organocatalysts frequently used in organic synthesis (proline, **II**; quinine, **III**; quinidine, **IV**; and diphenylprolinol, **V**).

We designed a different route based on the enantioselective halogenation of olefins by organocatalytic methods in order to obtain the required carvone epoxides. The halocyclization reactions have been a subject of interest for the organic chemist over the years [31]. Recently, the asymmetric halogenation of olefins has become an area of expansion, with many research groups interested in it [32–34].

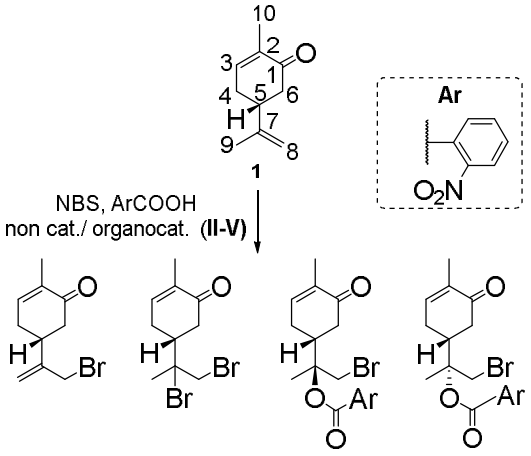
Due to the importance of the natural epoxides **3** and **4** for the synthesis of natural products [35], where they act as starting materials, there has been a great interest in their synthesis. Notwithstanding this, to the best of our knowledge, they have not been separated or obtained separately. In this work, we report the synthesis of the 7,8-epoxyderivatives **3** and **4** separately from the bromoester derivatives of carvone **7** and **8** using an organocatalysed procedure.

2. Results and Discussion

Due to the different reactivity of the two double bonds of carvone, the enantioselective bromo-alcohol functionalization of the terminal double bond can be achieved using an organocatalyst in acidic conditions. It has been known for a long time that the use of amino acids with NBS produces a bromine transfer into the amino acid, which, if chiral, could be used for enantioselective bromination [36]. It is also known that quinidine and quinine derivatives form complexes with halogen that have been used in enantioselective halocyclization reactions [37]. For these reasons,

we selected the organocatalysts of Figure 1 (**II**–**V**) to obtain the corresponding bromoderivatives, listed in Table 1. In this case, we decided to use acidic media to open the corresponding bromonium intermediate. First of all, the bromination reaction of carvone, **1**, was carried out by reaction with NBS and *o*-nitrobenzoic acid in order to facilitate the ester hydrolysis afterwards, and different organocatalysts, such as proline **II**, quinine **III**, quinidine **IV**, or diphenylprolinol **V**, using CH_2Cl_2 as the solvent (Table 1).

Table 1. Organocatalyst scope and optimization of reaction conditions for the synthesis of the bromoesters **7** and **8**.



Entry [a]	Catalyst, Load	T (°C)	Time (days)	Yield (%) [b]					d.r. (%) [c]
				1	**5**	**6**	**7**	**8**	
1	No catalyst	rt	6	15	28	-	15	12	11
2	No catalyst	39	3	15	27	-	18	16	6
3	Proline, **II,** 2%	rt	6	-	12	4	34	20	26
4	Proline, **II,** 20%	rt	6	-	13	5	36	18	33
5	Proline, **II,** 20%	39	6	-	17	-	34	18	31
6	Quinine, **III,** 2%	39	6	-	14	-	36	20	29
7	Quinine, **III,** 20%	rt	6	-	16	-	35	13	46
8	Quinine, **III,** 20%	39	6	-	17	-	36	16	38
9	Quinidine, **IV,** 2%	rt	6	-	13	-	56	11	67
10	Quinidine, **IV,** 2%	39	6	-	16	-	41	14	49
11	Quinidine, **IV,** 20%	rt	6	-	15	-	57	10	70
12	Quinidine, **IV,** 20%	39	6	-	11	-	54	16	54
13	Diphenylprolinol, **V,** 2%	rt	6	-	20	-	27	10	46
14	Diphenylprolinol, **V,** 2%	39	6	-	7	-	35	28	11
15	Diphenylprolinol, **V,** 20%	rt	6	-	21	-	50	17	50
16	Diphenylprolinol, **V,** 20%	39	6	-	23	-	44	24	29

[a] All reactions were carried out in CH_2Cl_2 at room temperature (r.t.) or heating at 39 °C. Reaction conditions ratio: *R*-carvone/NBS/*o*-nitrobenzoic acid 1/1.4/1.4. [b] Yields refer to isolated compounds; the remaining proportion to 100% comprises decomposition products. [c] Diastereoselection in d.r. was based on isolated compounds **7** and **8**.

As displayed in Table 1, when the reaction shown in Table 1 is carried out without a catalyst at room temperature (entry 1), the reaction is quite slow, giving mainly the allyl bromoderivative **5** and the mixture of the bromoesters **7** and **8** in relatively low yield, with carvone recovered in a 15% yield. To increase the reaction rate, the reaction was heated to 39 °C, finding no substantial increase in the yield of **7** or **8** (entry 2). Then, we carried out the organocatalysed reaction using proline **II**, quinine **III**, quinidine **IV**, or diphenylprolinol **V** at different temperatures and changing the load of catalyst. When proline **II** was used (entries 3–5), the yield in the required bromoesters (**7** and **8**), was increased with a moderated d.r., and no recovery of carvone was observed, also with a decrease in the quantity of the bromoderivative **5** produced. When the temperature was raised to 39 °C, the yield of the bromoesters **7** and **8** decreased, and also the diastereoselectivity. It is worth noticing that a

larger amount of organocatalyst increased the diastereoselectivity moderately, but when heated, the diastereoselectivity decreased. A small quantity of a subproduct was identified as a mixture (3:1) of dibromoderivative **6** when proline was used as the organocatalyst (entries 3 and 4); due to the small amount obtained, the stereochemistry of the major diastereomer has not been determined. When quinine **III** is used as the catalyst (entries 6–8), it does not increase the yield for the obtention of **7** and **8**, but an increase in the diastereoselectivity is achieved when a 20% load is used (entry 7), leading to a global yield of 48% for the bromoesters and a diastereoselectivity of 46%. When quinidine **IV** was used, it led to an increase in the yield and diastereoselectivity (entries 9–12); in particular, if 20% of quinidine **IV** was used at room temperature (entry 11), the yield of the bromoesters rose to 67% with a diastereoselectivity of 70%. When diphenylprolinol **V** was used as the organocatalyst (entries 13–16) the best results were observed at room temperature and at a 20% load (entry 15).

To sum up, our results show that the use of an organocatalyst enhances the yield for the obtention of the bromoesters **7** and **8**, leading to moderate or good diastereocontrol, depending on the catalyst used and its load.

The structures of all the compounds were determined by their spectroscopic properties, and the stereochemistry was established by X-ray diffraction of the crystal structures of the bromoester **7** and **8** (Figure 2) [38]. In this manner, there was not any doubt about the stereochemistry of these compounds.

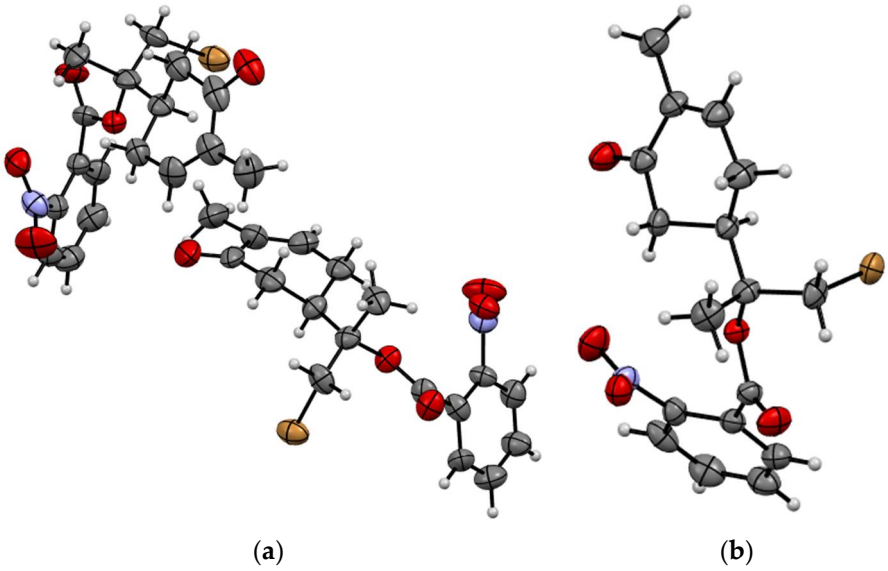


Figure 2. X-ray-determined structures of compounds: (**a**) bromoester **7** crystallised as dimers in the cell unit and (**b**) bromoester **8**. Atom colours: grey (C), white (H), blue (N), red (O) and light brown (Br).

To shed some light onto the mechanism of the reaction, we carried out a conformational study of the landscape associated with the dihedral angle between C8–C7–C4–C3 of *R*-carvone. In these calculations, the solvent CH_2Cl_2 was simulated using the polarisable continuum model (see Methods for further details). The results, depicted in Figure 3, show that there are three minima separated by low energy barriers that could be easily crossed at room temperature, as expected for the rotation along a single C–C bond. The most stable conformation corresponds to that with the side chain perpendicular to the phenyl ring and with the methyl group *anti* to the H of C5. Interestingly, the structure with the methyl group *syn* to the H of C5 corresponds to a maximum (both structures are shown in Figure 3). The structure of the three minima correspond to those found by Avilés and coworkers [39] for *S*-carvone, although there are some differences in the barrier heights that separate them, probably due to the different *ab initio* method used and the fact that no solvent was included in the simulations of the Ref. [39].

Using the *ab initio* calculations, we could estimate that at 39 °C, *R*-carvone populates 58% of the lowest energy rotamer. These results are in good agreement with the experimental results in Table 1, explaining why only a modest stereoselectivity was achieved in the absence of catalysts.

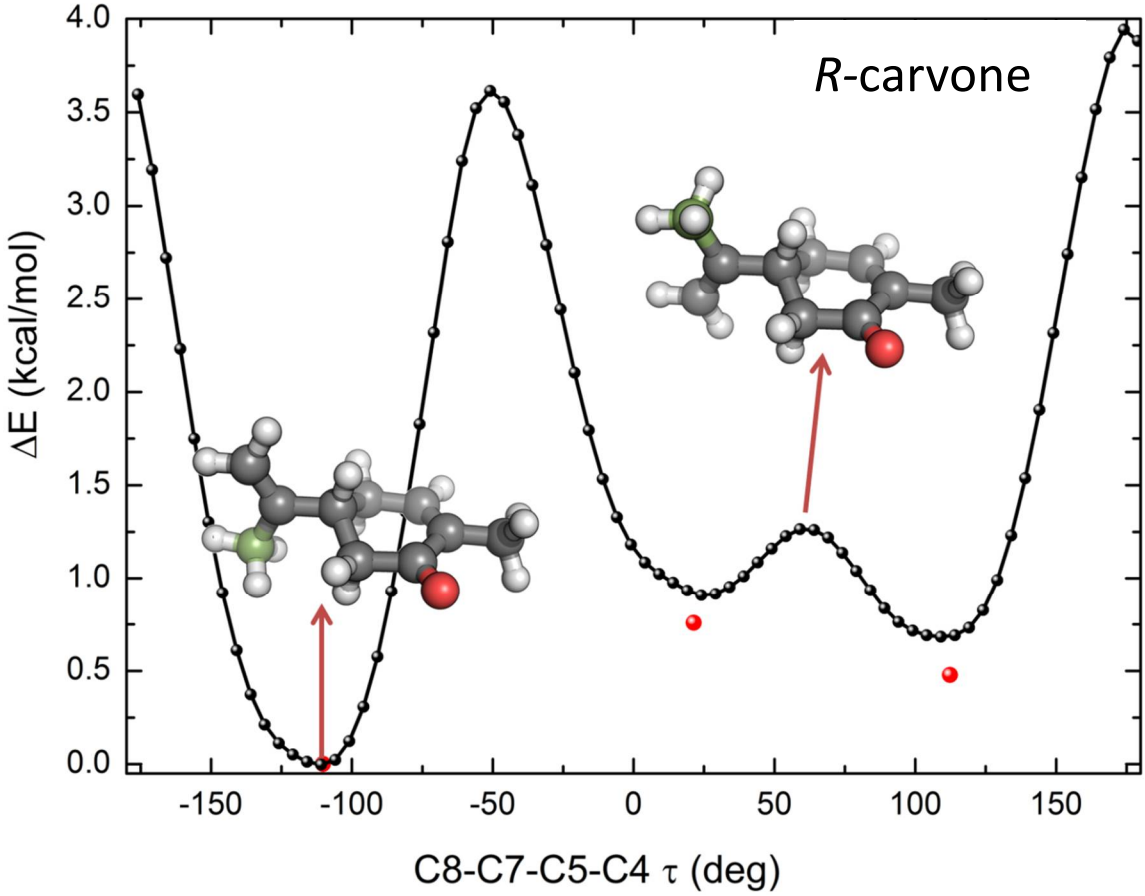


Figure 3. Scan of the potential energy surface calculated along the C8–C7–C4–C3 of *R*-carvone at a MP2/6-31+G(d,p) level of theory (black points). The minima were further optimized at a MP2/6-311++G(d,p) level of theory and their relative energies are also shown as red points. The structures corresponding to the global minimum and the transition state between the two local minima are shown as spheres (red (O), white (H), grey (C), to highlight the difference between both conformers C9 is shown in green). (See text for further details).

Keeping in mind this conformational analysis, we suggest the reaction mechanism displayed in Figure 4, where a hydrogen bond between the carbonyl group of carvone and the hydroxyl group of the organocatalyst stabilizes the complex **VI**, leading to a bromination of the alpha side and the entry of the nucleophile by the beta side, as shown in Figure 4.

The bromoester derivatives **7** and **8** are intermediates in the synthesis of the epoxy derivatives of carvone. The hydrolysis reaction of **7** and **8** with alkali grants the synthesis of the epoxy derivatives **3** and **4**, respectively (see Scheme 2).

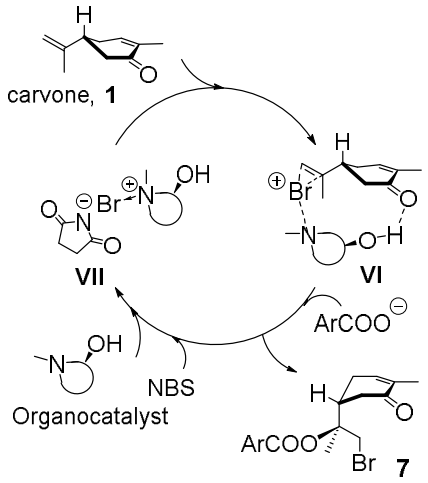
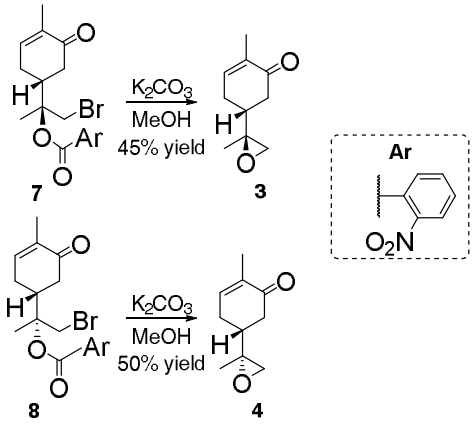


Figure 4. Proposed mechanism for the observed stereochemical outcome.



Scheme 2. Synthesis of 7,8-carvone epoxides **3** and **4**. Further research using *S*-carvone is in process in order to test the possible match–mismatch diastereoselectivity.

3. Materials and Methods

3.1. Reagents

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. Diethyl ether, tetrahydrofuran and benzene were distilled from sodium and benzophenone under argon atmosphere; dichloromethane and pyridine were distilled from calcium hydride under argon atmosphere.

3.2. Characterization

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 400 MHz DRX (400 MHz ^{1}H and 100 MHz ^{13}C) (Bruker Biospin, Wissembourg, France) and a VARIAN 200 (200 MHz ^{1}H and 50 MHz ^{13}C) (Varian Inc, Palo Alto, California, USA). Chemical shifts are expressed in δ (ppm) and coupling constants (*J*) are given in Hz. All spectra were performed in $CDCl_3$ as solvent and referenced to the residual peak of $CHCl_3$ at δ = 7.26 ppm for ^{1}H and δ = 77.0 ppm for ^{13}C.

X-Ray Crystallography

Single crystals of **7** and **8** for XRD (X-ray diffraction) analysis were obtained by slow evaporation of a solution in hexane/CH_2Cl_2 (98:2) at room temperature. X-ray diffraction intensity data were collected for **7** and **8** compounds on a Bruker Kappa Apex II single crystal X-ray diffractometer (Bruker

AXS Inc, Madison, Wisconsin, USA), equipped with graphite monochromator, CuK_α (λ = 1.54178 Å) radiation and CCD detector. Suitable single crystals were mounted on a glass fiber using cyanoacrylate adhesive. The unit cell parameters were determined by collecting the diffracted intensities from 36 frames measured in three different crystallographic zones and using the method of difference vectors. Typical data sets consist of combinations of ω and ϕ scan frames with a typical scan width of 0.5° and an exposure time of 10 s/frame at a crystal-to-detector distance of ~4.0 cm. The collected frames were integrated with the SAINT software package (SAINT, Bruker AXS Inc, Madison, Wisconsin, USA) using a narrow-frame algorithm. Final cell constants were determined by the global refinement of reflections from the complete data set. Data were corrected for absorption effects using the multiscan method implemented in SADABS. Structure solutions and refinement were carried out using the SHELXTL software package (SHELXTL, Bruker AXS Inc, Madison, Wisconsin, USA). The structures were solved by direct methods combined with difference Fourier synthesis and refined by full-matrix least-squares procedures, with anisotropic thermal parameters in the last cycles of refinement for all non-hydrogen atoms. The hydrogen atoms were positioned geometrically.

3.3. Computational Methods

Electronic structure calculations were carried out using the Gaussian09 [40] suite of programs on *R*-carvone. The dihedral angle between C8, C7, C5, and C4 was scanned at a MP2/6-31+G(d,p) level of theory, finding three minima whose structures were further optimized at a MP2/6-311++G(d,p) level of theory. The frequencies corresponding to the three structures were calculated to ensure that they correspond to minima of the potential energy surface. Solvation effects were including using the polarizable continuum model [41] with the standard dielectric constant of 8.93 for dichloromethane. The geometry of the global minimum is given in Table 2.

To rationalize the population of *R*-carvone in the surroundings of each minima, we calculated the canonical partition function, considering that each of the aforementioned scanned points corresponded to one different state.

Table 2. Coordinates of the global minimum: (MP2/6-31++G(d,p), E(Eh) = −463.43093).

C	3.166	−0.027	1.285
C	2.926	0.247	−1.184
C	−3.461	−0.554	0.118
C	−1.150	−1.514	−0.146
C	0.348	−1.433	−0.231
C	0.098	1.040	−0.298
C	2.369	0.033	0.201
C	−1.967	−0.440	−0.014
C	−1.386	0.926	−0.015
C	0.872	−0.114	0.351
O	−2.090	1.917	0.171
H	0.447	2.017	0.051
H	0.223	1.001	−1.390
H	−3.961	−0.011	−0.690
H	−3.797	−0.111	1.060
H	−3.771	−1.601	0.089
H	−1.600	−2.507	−0.186
H	0.791	−2.283	0.303
H	0.654	−1.530	−1.284
H	0.638	−0.116	1.425
H	2.587	1.203	−1.599
H	4.019	0.254	−1.163
H	2.600	−0.538	−1.875
H	2.751	−0.168	2.280
H	4.246	0.062	1.197

4. Experimental Section

4.1. General Procedure for the Synthesis of the Bromoesters **7** *and* **8**

To a solution of catalyst (2% or 20%) in 20 mL of CH_2Cl_2, carvone **1** (1.00 g, 6.66 mmol), nitrobenzoic acid (1.56 g, 9.32 mmol), and *N*-bromosuccinimide (1.66 g, 9.32 mmol) were added. The reaction mixture was stirred for 6 days at room temperature or at 39 °C. After that, the solvent was evaporated and the resulting crude product was purified by chromatography on silica gel (*n*-hexane/EtOAc) to provide the isolated compounds: **5**, **6**, **7** and **8**.

Example of synthetic protocol to access diastereomers esters **7** and **8**, entry 3, Table 1:

Nitrobenzoic acid (1.56 g, 9.34 mmol) and *N*-bromosuccinimide (1.66 g, 9.38 mmol) were added to a solution containing proline **II** (15.3 mg, 0.13 mmol, 2% load) and carvone **1** (1.00 g, 6.66 mmol) in 20 ml of CH_2Cl_2. The resulting mixture was stirred for 6 days at given temperature, and then the solvent was removed under vacuum and the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 7:3) to yield separately the desired bromoesters **7** (34%) and **8** (20%), d.r. 26%, and the side product was identified as the alkyl bromo derivative **5** (16%), together with the dibromoester compound **6** in a very low yield (4%).

4.1.1. (5*R*)-9-Bromocarvone (**5**)

(*n*-hexane/EtOAc, 9:1) (243.2 mg, 16%). $[\alpha]_D^{20} = -6.8$ (*c* = 1.46 in $CHCl_3$); IR (film) ν: 3419, 2976, 2937, 1746, 1709, 1663, 1382, 1220, 1058, 950; ^{1}H NMR (400 MHz $CDCl_3$,): δ = 6.72 (1H, ddd, *J* = 6.1, 3.0, 1.6 Hz, H-3), 5.26 (1H, s, Ha-8), 5.01 (1H, d, *J* = 1.3 Hz, Hb-8), 3.97 (2H, d, *J* = 2.0 Hz, H-9), 2.97 (1H, ddd, *J* = 14.4 Hz, 10.0, 4.6 Hz, H-5), 2.61 (1H, m, Ha-6), 2.53 (1H, m, Ha-4), 2.34 (1H, dd, *J* = 16.0, 12.9 Hz, Hb-6), 2.27 (1H, m, Hb-4), 1.74 (3H, s, H-10); ^{13}C NMR (100 MHz, $CDCl_3$,): δ = 199.0, 147.0, 144.2, 135.7, 115.8, 43.3, 38.2, 35.2, 31.6, 15.8; HRMS (EI) *m*/*z* calculated for $C_{10}H_{14}BrO$ 229.0223 ($M + H^+$) found 229.0222.

4.1.2. (5*R*,7*RS*)-7,8-Dibromocarvone (**6**)

(*n*-hexane/EtOAc, 95:5) (82.0 mg, 4%). $[\alpha]_D^{20} = -10.6$ (*c* = 1.88 mixture of diastereomers 3/1 in $CHCl_3$); IR (film) ν: 2980, 2923, 1668, 1380, 1257, 1083, 1060, 904, 711; ^{1}H NMR (400 MHz $CDCl_3$,): δ = 6.71 (1H, dt, *J* = 15.0, 4.6 Hz, H-6), 3.93 (1H, m, Ha-8), 3.82 (1H, d, *J* = 10.3 Hz, Hb-8), 2.60 (2H, m, H-6), 2.42 (3H, m, H-5), 1.84 (3H, s, H-9), 1.76 (s, 3H, H-10); ^{13}C NMR (100 MHz, $CDCl_3$,): δ = 198.4, 143.4, 135.3, 71.0, 42.3, 40.7, 40.6, 28.8, 27.9, 15.6; HRMS (EI) *m*/*z* calculated for $C_{10}H_{16}Br_2O$ 308.9484 ($M + H^+$) found 308.9479.

4.1.3. (5*R*,7*R*)-8-Bromo-7-(2-nitrobenzoate)carvone (**7**)

(*n*-hexane/EtOAc, 7:3) (898.1 mg, 34%). $[\alpha]_D^{20} = +41.7$ (*c* = 0.48 in $CHCl_3$); IR (film) ν: 1728, 1668, 1530, 1348, 1289, 1255, 1123, 1066, 908, 733, 730; ^{1}H NMR (400 MHz $CDCl_3$,): δ = 7.91 (1H, dd, *J* = 8.0, 1.2 Hz, H-6′), 7.72 (1H, m, H-5′), 7.64 (1H, m, H-4′), 7.61 (1H, m, H-3′), 6.74 (1H, m, H-3), 4.06 (1H, d, *J* = 11.1 Hz, Ha-8), 4.01 (1H, d, *J* = 11.1 Hz, Hb-8), 2.82 (1H, m, H-5), 2.50 (1H, m, Ha-6), 2.43 (1H, m, Ha-4), 2.29 (1H, m, Hb-6), 2.20 (1H, dd, *J* = 15.9, 14.2 Hz, Hb-4), 1.74 (s, 3H, H-10), 1.72 (s, 3H, H-9); ^{13}C NMR (100 MHz, $CDCl_3$,): δ = 198.1, 164.4, 147.3, 144.5, 135.3, 133.4, 131.6, 129.7, 128.5, 124.0, 85.4, 41.0, 38.5, 35.4, 26.1, 19.0, 15.6; HRMS (EI) *m*/*z* calculated for $C_{17}H_{18}BrNO_5Na$ 418.0260 ($M + Na^+$) found 418.0265.

Crystal data for **7**: $C_{17}H_{18}BrNO_5$, M = 396.23, monoclinic, space group P_{21} (n° 4), a = 8.0408(6) Å, b = 28.336(2) Å, c = 8.1290(6) Å, α = γ = 90°, β = 103.603(4)°, V = 1800.2(2) Å3, Z = 4, D_c = 1.462 Mg/m^3, m = (Cu-K_α) = 3.340 mm^{-1}, F(000) = 808. 10420 reflections were collected at 3.12 ≤ 2θ ≤ 67.40 and merged to give 4916 unique reflections (R_{int} = 0.0872), of which 2992 with I > σ (I) were considered to be observed. Final values are R = 0.0765, *w*R = 0.2113, GOF = 1.026, max/min residual electron density 0.703 and −0.652 e. Å^{-3}.

4.1.4. (5*R*,7*S*)-8-Bromo-7-(2-nitrobenzoate)carvone (**8**)

(*n*-hexane/EtOAc, 7:3) (528.3 mg, 20%). $[\alpha]_D^{20}$ = +6.9 (*c* = 1.44 in $CHCl_3$); IR (film) ν: 1728, 1668, 1530, 1348, 1289, 1255, 1123, 1066, 908, 733, 711; ^{1}H NMR (400 MHz $CDCl_3$,): δ = 7.91 (1H, d, *J* = 7.7 Hz, H-6′), 7.66 (1H, m, H-5′), 7.65 (1H, m, H-4′), 7.61 (1H, m, H-3′), 6.68 (1H, m, H-3), 4.15 (1H, d, *J* = 11.2 Hz, Ha-8), 3.90 (1H, d, *J* = 11.2 Hz, Hb-8), 2.82 (1H, m, H-5), 2.58 (1H, m, Ha-6), 2.36 (1H, m, Ha-4), 2.24 (1H, dd, *J* = 15.8, 14.7 Hz, Hb-6), 2.19 (1H, m, Hb-4), 1.72 (3H, s, H-9), 1.71 (3H, s, H-10); ^{13}C NMR (100 MHz, $CDCl_3$,): δ = 198.5, 164.4, 147.1, 143.4, 135.6, 133.4, 133.1, 129.5, 128.5, 124.0, 85.2, 40.9, 38.2, 35.5, 26.3, 18.7, 15.6; HRMS (EI) *m*/*z* calculated for $C_{17}H_{18}BrNO_5Na$ 418.0266 (M + Na^+) found 418.0265. See Figure 1 for X-ray.

Crystal data for **8**: $C_{17}H_{18}BrNO_5$, M = 396.22, monoclinic, space group P_{21} (n° 4), a = 7.7282(4) Å, b = 13.9571(11) Å, c = 8.5804(6) Å, α = γ = 90°, β = 109.037(5)°, V = 874.89(11) $Å^3$, Z = 2, D_c = 1.504 Mg/m^3, m = (Cu-K_α) = 3.437 mm^{-1}, F(000) = 404. 3704 reflections were collected at $5.45 \leq 2\theta \leq 65.91$ and merged to give 2154 unique reflections (R_{int} = 0.0351), of which 1799 with I > σ (I) were considered to be observed. Final values are R = 0.0491, *w*R = 0.1280, GOF = 1.062, max/min residual electron density 0.417 and −0.716 e. $Å^{-3}$.

4.2. Hydrolysis Reaction of Bromoesters **7** *and* **8**

In a round-bottom flask equipped with a reflux condenser, compound **7** or **8**, MeOH (20 mL), and K_2CO_3 (0.1 mmol) were added. The resulting mixture was stirred at 35 °C and the progress of the reaction was monitored by thin-layer chromatography (TLC). The solvent was evaporated, and finally, the reaction product was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 8:2) to obtain compound **3** (45%) or **4** (50%), respectively.

4.2.1. (5*R*,7*S*)-7,8-Epoxycarvone (**3**)

$[\alpha]_D^{20}$ = −13.5 (*c* = 0.74 in $CHCl_3$); IR (film) ν: 2980, 2924, 1667, 1450, 1382, 1106, 901, 834, 704; ^{1}H NMR (400 MHz $CDCl_3$,): δ = 6.72 (m, 1H, H-3), 2.65 (d, *J* = 4.6 Hz, 1H, Ha-8), 2.61 (d, *J* = 4.6 Hz, 1H, Hb-8), 2.58 (m, 1H, Ha-6), 2.51 (m, 1H, Hb-6), 2.38 (m, 1H Ha-4), 2.25 (m, 1H, Hb-4), 2.06 (m, 1H, H-5), 1.77 (s, 3H, H-10), 1.29 (s, 3H, H-9); ^{13}C NMR (100 MHz, $CDCl_3$,): δ = 198.2, 144.2, 135.6, 58.0, 52.9, 41.3, 40.4, 27.7, 18.4, 15.7; HRMS (EI) *m*/*z* calculated for $C_{10}H_{14}O_2Na$ 189.0886 (M + Na^+) found 189.0891.

4.2.2. (5*R*,7*R*)-7,8-Epoxycarvone (**4**)

$[\alpha]_D^{20}$ = +12.8 (*c* = 0.74 in $CHCl_3$); IR (film) ν: 2980, 2924, 1667, 1450, 1382, 1106, 901, 834, 704; ^{1}H NMR (400 MHz $CDCl_3$,): δ = 6.73 (m, 1H, H-3), 2.72 (d, *J* = 4.5 Hz, 1H, Ha-8), 2.58 (d, *J* = 4.5 Hz, 1H, Hb-8), 2.55 (m, 1H, Ha-6), 2.06 (m, 1H, H-5), 2.17 (m, 3H, Hb-6, Ha-4, Hb-4) 1.76 (s, 3H, H-10), 1.31 (s, 3H, H-9); ^{13}C NMR (100 MHz, $CDCl_3$,): δ = 199.1, 144.1, 135.6, 57.9, 52.4, 40.7, 39.9, 27.9, 19.0, 15.7; HRMS (EI) *m*/*z* calculated for $C_{10}H_{14}O_2Na$ 189.0886 (M + Na^+) found 189.0891.

5. Conclusions

Throughout this article, we have developed a novel method for the selective synthesis of 7,8-carvone epoxy derivatives. The diastereoselective synthesis of these epoxides from carvone in two steps with bromoester intermediates using organocatalysis has been achieved. To the best of our knowledge, it is the first time that these epoxides have been obtained separately; and due to their synthetic potential, this methodology can be used for the enantioselective synthesis of many natural products.

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References and Note

1. Finkbeiner, P.; Murai, K.; Röpke, M.; Sarpong, R. Total synthesis of terpenoids employing a "benzannulation of carvone" strategy: Synthesis of (−)-crotogoudin. *J. Am. Chem. Soc.* **2017**, *139*, 11349–11352. [CrossRef] [PubMed]
2. Nannini, L.J.; Nemat, S.J.; Carreira, E.M. Total synthesis of (+)-sarcophytin. *Angew. Chem. Int. Ed.* **2018**, *57*, 823–826. [CrossRef] [PubMed]
3. Kobayashi, K.; Kunimura, R.; Takagi, H.; Hirai, M.; Kogen, H.; Hirota, H.; Kuroda, C. Total synthesis of highly oxygenated bisabolane sesquiterpene isolated from ligularia lankongensis: Relative and absolute configurations of the natural product. *J Org Chem* **2018**, *83*, 703–715. [CrossRef] [PubMed]
4. Senthil Kumaran, R.; Mehta, G. A versatile, rcm based approach to eudesmane and dihydroagarofuran sesquiterpenoids from (−)-carvone: A formal synthesis of (−)-isocelorbicol. *Tetrahedron* **2015**, *71*, 1718–1731. [CrossRef]
5. Abad, A.; Agulló, C.; Cuñat, A.C.; Llosá, M.C. Stereoselective construction of the tetracyclic scalarane skeleton from carvone. *Chem. Commun.* **1999**, 427–428. [CrossRef]
6. Abad, A.; Agulló, C.; Cuñat, A.; De Alfonso, I.; Navarro, I.; Vera, N. Synthesis of highly functionalised enantiopure bicyclo[3.2.1]-octane systems from carvone. *Molecules* **2004**, *9*, 287–299. [CrossRef] [PubMed]
7. Mak, K.K.W.; Lai, Y.M.; Siu, Y.-H. Regiospecific epoxidation of carvone: A discovery-oriented experiment for understanding the selectivity and mechanism of epoxidation reactions. *J. Chem. Ed.* **2006**, *83*, 1058. [CrossRef]
8. Masarwa, A.; Weber, M.; Sarpong, R. Selective c–c and c–h bond activation/cleavage of pinene derivatives: Synthesis of enantiopure cyclohexenone scaffolds and mechanistic insights. *J. Am. Chem. Soc.* **2015**, *137*, 6327–6334. [CrossRef] [PubMed]
9. Valeev, R.F.; Bikzhanov, R.F.; Selezneva, N.K.; Gimalova, F.A.; Miftakhov, M.S. Synthesis of 6-hydroxycarvone derivatives and their oxidative decyclization with lead tetraacetate. *Russ. J. Org. Chem.* **2011**, *47*, 1287. [CrossRef]
10. Sepúlveda-Arias, J.C.; Veloza, L.A.; Escobar, L.M.; Orozco, L.M.; Lopera, I.A. Anti-inflammatory effects of the main constituents and epoxides derived from the essential oils obtained from tagetes lucida, cymbopogon citratus, lippia alba and eucalyptus citriodora. *J. Essent. Oil Res.* **2013**, *25*, 186–193. [CrossRef]
11. Kimbaris, A.C.; González-Coloma, A.; Andrés, M.F.; Vidali, V.P.; Polissiou, M.G.; Santana-Méridas, O. Biocidal compounds from mentha sp. Essential oils and their structure–activity relationships. *Chem. Biodivers.* **2017**, *14*. [CrossRef] [PubMed]
12. Mandelli, D.; Kozlov, Y.N.; da Silva, C.A.R.; Carvalho, W.A.; Pescarmona, P.P.; Cella, D.d.A.; de Paiva, P.T.; Shul'pin, G.B. Oxidation of olefins with H_2O_2 catalysed by gallium(III) nitrate and aluminum(III) nitrate in solution. *J. Mol. Catal. A Chem.* **2016**, *422*, 216–220. [CrossRef]
13. Kamata, K.; Sugahara, K.; Yonehara, K.; Ishimoto, R.; Mizuno, N. Efficient epoxidation of electron-deficient alkenes with hydrogen peroxide catalysed by $[\gamma\text{-}PW_{10}O_{38}V_2(\mu\text{-}OH)_2]^{3-}$. *Chemistry* **2011**, *17*, 7549–7559. [CrossRef] [PubMed]
14. Gomez, L.; Garcia-Bosch, I.; Company, A.; Sala, X.; Fontrodona, X.; Ribas, X.; Costas, M. Chiral manganese complexes with pinene appended tetradentate ligands as stereoselective epoxidation catalysts. *Dalton Trans.* **2007**, 5539–5545. [CrossRef] [PubMed]

15. Yu, S.; Miao, C.-X.; Wang, D.; Wang, S.; Xia, C.; Sun, W. Mnii complexes with tetradentate n4 ligands: Highly efficient catalysts for the epoxidation of olefins with H_2O_2. *J. Mol. Catal. A Chem.* **2012**, *353–354*, 185–191. [CrossRef]
16. Garcia-Bosch, I.; Ribas, X.; Costas, M. A broad substrate-scope method for fast, efficient and selective hydrogen peroxide-epoxidation. *Adv. Syn. Catal.* **2009**, *351*, 348–352. [CrossRef]
17. Spannring, P.; Yazerski, V.A.; Chen, J.; Otte, M.; Weckhuysen, B.M.; Bruijnincx, P.C.A.; Klein Gebbink, R.J.M. Regioselective cleavage of electron-rich double bonds in dienes to carbonyl compounds with [Fe(OTf)$_2$(mix-BPBP)] and a combination of H_2O_2 and $NaiO_4$. *Eur. J. Inorg. Chem.* **2015**, *2015*, 3462–3466. [CrossRef]
18. Oddon, F.; Girgenti, E.; Lebrun, C.; Marchi-Delapierre, C.; Pécaut, J.; Ménage, S. Iron coordination chemistry of N_2Py_2 ligands substituted by carboxylic moieties and their impact on alkene oxidation catalysis. *Eur. J. Inorg. Chem.* **2012**, *2012*, 85–96. [CrossRef]
19. Clemente-Tejeda, D.; López-Moreno, A.; Bermejo, F.A. Non-heme iron catalysis in C=C, C–H, and CH_2 oxidation reactions. Oxidative transformations on terpenoids catalysed by Fe(bpmen)(OTf)$_2$. *Tetrahedron* **2013**, *69*, 2977–2986. [CrossRef]
20. Yazerski, V.A.; Spannring, P.; Gatineau, D.; Woerde, C.H.M.; Wieclawska, S.M.; Lutz, M.; Kleijn, H.; Klein Gebbink, R.J.M. Making Fe(BPBP)-catalysed C-H and C=C oxidations more affordable. *Org. Biomol. Chem.* **2014**, *12*, 2062–2070. [CrossRef] [PubMed]
21. Thatte, C.S.; Rathnam, M.V.; Kumar, M.S.S. Synthesis, characterization and application of chitosan based schiff base-transition metal complexes (Mn, Cu, Co, Ni). *JOAC* **2013**, *2*, 1192.
22. Stok, J.E.; Yamada, S.; Farlow, A.J.; Slessor, K.E.; De Voss, J.J. Cytochrome P450$_{cin}$ (CYP176A1) D241N: Investigating the role of the conserved acid in the active site of cytochrome P450s. *Biochim. Biophys. Acta* **2013**, *1834*, 688–696. [CrossRef] [PubMed]
23. Méndez-Sánchez, D.; Ríos-Lombardía, N.; Gotor, V.; Gotor-Fernández, V. Chemoenzymatic epoxidation of alkenes based on peracid formation by a rhizomucor miehei lipase-catalysed perhydrolysis reaction. *Tetrahedron* **2014**, *70*, 1144–1148. [CrossRef]
24. Rodilla, J.M.; Neves, P.P.; Pombal, S.; Rives, V.; Trujillano, R.; Díez, D. Hydrotalcite catalysis for the synthesis of new chiral building blocks. *Nat. Prod. Res.* **2016**, *30*, 834–840. [CrossRef] [PubMed]
25. Majetich, G.; Shimkus, J.; Li, Y. Epoxidation of olefins by β-bromoalkoxydimethylsulfonium ylides. *Tetrahedron Lett.* **2010**, *51*, 6830–6834. [CrossRef]
26. Dalko, P.I.; Moisan, L. Enantioselective organocatalysis. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748. [CrossRef]
27. List, B. Asymmetric aminocatalysis. *Synlett* **2001**, *2001*, 1675–1686. [CrossRef]
28. Brown, S.P.; Brochu, M.P.; Sinz, C.J.; MacMillan, D.W.C. The direct and enantioselective organocatalytic α-oxidation of aldehydes. *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809. [CrossRef] [PubMed]
29. Pidathala, C.; Hoang, L.; Vignola, N.; List, B. Direct catalytic asymmetric enolexo aldolizations. *Angew. Chem. Int. Ed.* **2003**, *42*, 2785–2788. [CrossRef] [PubMed]
30. MacMillan, D. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, Germany, 2005; p. 454.
31. Jiang, X.; Liu, H. 4.07 electrophilic cyclization a2-knochel, paul. In *Comprehensive Organic Synthesis II*, 2nd ed.; Elsevier: Amsterdam, The Netherlands, 2014; pp. 412–494.
32. Bar, S. Organocatalysis in the stereoselective bromohydrin reaction of alkenes. *Can. J. Chem.* **2010**, *88*, 605–612. [CrossRef]
33. Castellanos, A.; Fletcher, S.P. Current methods for asymmetric halogenation of olefins. *Chem. Eur. J.* **2011**, *17*, 5766–5776. [CrossRef] [PubMed]
34. Tan, C.K.; Yeung, Y.-Y. Recent advances in stereoselective bromofunctionalization of alkenes using n-bromoamide reagents. *Chem. Commun.* **2013**, *49*, 7985–7996. [CrossRef] [PubMed]
35. Valeev, R.F.; Bikzhanov, R.F.; Yagafarov, N.Z.; Miftakhov, M.S. Synthesis of the northern fragment of an epothilone d analogue from (−)-carvone. *Tetrahedron* **2012**, *68*, 6868–6872. [CrossRef]
36. Antelo, J.M.; Arce, F.; Crugeiras, J. Kinetics of electrophilic bromine transfer from n-bromosuccinimide to amines and amino acids. *J. Chem. Soc. Perk. Trans.* **1995**, *2*, 2275–2279. [CrossRef]
37. Chen, G.; Ma, S. Enantioselective halocyclization reactions for the synthesis of chiral cyclic compounds. *Angew. Chem. Int. Ed.* **2010**, *49*, 8306–8308. [CrossRef] [PubMed]

38. Crystallographic data for the structures reported in this paper has been deposited at the Cambridge Crystallographic Data Centre as supplementary material No. CCDC 1821654–1821653 the data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.
39. Avilés Moreno, J.R.; Huet, T.R.; González, J.J.L. Conformational relaxation of s-(+)-carvone and r-(+)-limonene studied by microwave fourier transform spectroscopy and quantum chemical calculations. *Struct. Chem.* **2013**, *24*, 1163–1170. [CrossRef]
40. Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Scalmani, G.; Barone, V.; Petersson, G.A.; Nakatsuji, H.; et al. *Gaussian 09 rev. B.01*; Gaussian Inc.: Wallingford, CT, USA, 2009.
41. Scalmani, G.; Frisch, M.J. Continuous surface charge polarizable continuum models of solvation. I. General formalism. *J. Chem. Phys.* **2010**, *132*, 114110. [CrossRef] [PubMed]