Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2805–2810

TETRAHEDRON:
ASYMMETRY

The chemistry of zerumbone. Part 3: Stereospecific creation of five stereogenic centers by double Sharpless oxidation

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Received 28 September 2001; accepted 29 October 2001

Abstract—The Sharpless asymmetric epoxidation was applied to zerumbol **2** in order to introduce chirality into the readily available achiral sesquiterpene zerumbone **1**. Single bisepoxides (+)-**3** and (–)-**3** were obtained in nearly 100% enantiomeric purity, characterized as the unexpected all *erythro* configuration by X-ray analysis. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Zerumbone (2,6,10-humulatrien-1-one, **1**), the main constituent of the essential oil of the wild ginger, *Zingiber zerumbet* Smith,[1] is a monocyclic sesquiterpene containing a cross-conjugated dienone moiety. It exhibits a variety of interesting reactions, e.g. transannular ring contraction[2] and cyclization,[3] regio- and stereoselective conjugate additions,[2] and various regiospecific ring-cleavage reactions.[4] Much of its chemistry remains to be explored in order to fully exploit the ready availability and versatility of this substance as a starting material for conversion to other useful compounds. We have already noted,[2] for example, the possibility of employing zerumbone as a precursor of paclitaxel. Because zerumbone is achiral, we sought to introduce asymmetry through the application of the Sharpless–Katsuki asymmetric epoxidation of the allylic alcohol, zerumbol **2**. Sharpless et al. reported in 1980 the asymmetric epoxidation of allylic alcohols in high enantiomeric excess (e.e.), using the $Ti(OPr^i)_4$/optically active diethyl tartrate (DET)/*t*-butyl hydroperoxide (TBHP) system.[5] They demonstrated that the same system could be applied to the kinetic resolution of secondary allylic alcohols.[6] This epoxidation is now established as one of the most powerful methods for the introduction of stereogenic centers into a wide variety of prochiral allylic alcohols. Sharpless showed the *erythro* selectivity of epoxidation using titanium catalysts. When divinylmethanol derivatives are subjected to Sharpless kinetic resolution with one equivalent of oxidant, two chiral monoepoxides are obtained.[7] To obtain an *erythro* bisepoxide, one of the monoepoxy alcohols formed at less than 50% conversion using (+)- or (–)-DET is subjected to a second asymmetric epoxidation using the tartrate of opposite chirality.[6] We report our finding that zerumbol **2**, a racemic unsymmetrical divinylmethanol derivative, affords only a chiral all-*erythro* bisepoxide under Sharpless conditions using stoichiometric amounts of $Ti(OPr^i)_4$, TBHP, and either (+)- or (–)-DET.

2. Results and discussion

Zerumbone **1** was reduced with lithium aluminum hydride to afford alcohol **2** in quantitative yield. On treatment with 1.0 equiv. of $Ti(O^iPr)_4$, 1.2 equiv. of L-DET and 2.0 equiv. of TBHP at –30°C for 14 h in dichloromethane, **2** was converted to a single bisepoxide (–)-**3** in 40% yield with >99% e.e. (determined by ^1H NMR analysis using the chiral shift reagent $Eu(hfc)_3$) (Scheme 1). Monoepoxides were not detected and no alcohol **2** was recovered.

An orthorhombic crystal of (–)-**3** was obtained by recrystallization from hexane, allowing the structure to be determined by single-crystal X-ray analysis. (–)-**3**

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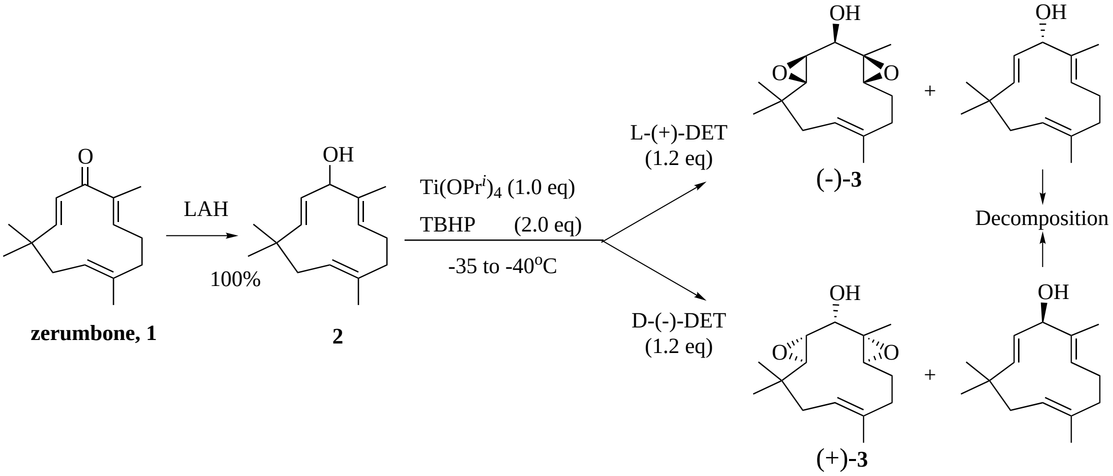
PII: S0957-4166(01)00505-5



Scheme 1.

crystallizes in space group $P2_12_12_1$, and the three oxygens are all located on the same face, the all-*erythro* form. Use of the enantiomeric tartrate, D-DET, under the same conditions gave the antipode (+)-**3** in 35% yield and >99% e.e., characterized by NMR, specific rotation, and single-crystal X-ray analysis (Fig. 1).

The effect of reaction conditions on stereoselectivity is shown in Table 1. With only TBHP or Ti(OPr^i)$_4$ no reaction occurred (runs 12 and 13), but the combination of these two reagents gave racemic bisepoxide **3** (run 11). Pure L- or D-DET gave almost enantiomerically pure **3** (runs 3 and 8), but the enantioselectivity reduced with prolonged reaction time or using reagents in excess or less than stoichiometric quantities (runs 5–7). The optimum reaction time was determined to be 14 h (runs 1–5). The use of racemic DET led to (±)-**3** (run 9), suggesting that the reaction velocity of chiral synthesis with L-DET is the same as that with D-DET. Substitution of the metal complex VO(acac)$_2$ gave the opposite *erythro* bisepoxide but in much lower e.e. (run 14).

As shown in Scheme 2, the absolute configurations of (−)-**3** and (+)-**3** were determined by anomalous dispersion of heavy atom derivatives. For this purpose the antipodes of **3** were converted to their *p*-chlorobenzoate esters, (−)- and (+)-**4**.

Trigonal crystals were obtained by recrystallization from hexane and subjected to X-ray analysis. (−)-**4** was shown to be the (1*R*,2*S*,3*R*,10*S*,11*R*)-isomer and (+)-**4** the (1*S*,2*R*,3*S*,10*R*,11*S*)-enantiomer. Chiral epoxidation of zerumbol gave an all-*erythro* bisepoxide from a single enantiomer of DET (Fig. 2). It is presumed that this novel result is due to conformational restrictions enforced by the medium ring, bringing the two reacting double bonds to the same order of reactivity.

3. Conclusions

Sharpless epoxidation converts the readily accessible zerumbone into a derivative containing five stereogenic centers in an all-*erythro* configuration, and offers exciting possibilities for providing chiral building blocks for the synthesis of useful physiologically active compounds. Crystallographic details for (−)-**3**, (+)-**4** and (−)-**4** have been deposited with the Cambridge Crystallographic Data Centre.

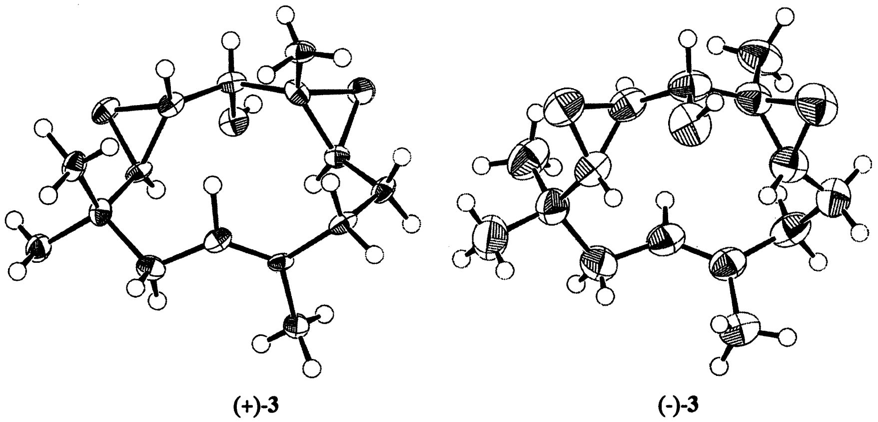


Figure 1. ORTEP drawing of the crystal structure of diepoxy alcohols (+)-**3** and (−)-**3**.

Table 1. Sharpless asymmetric diepoxidation of zerumbol **2**

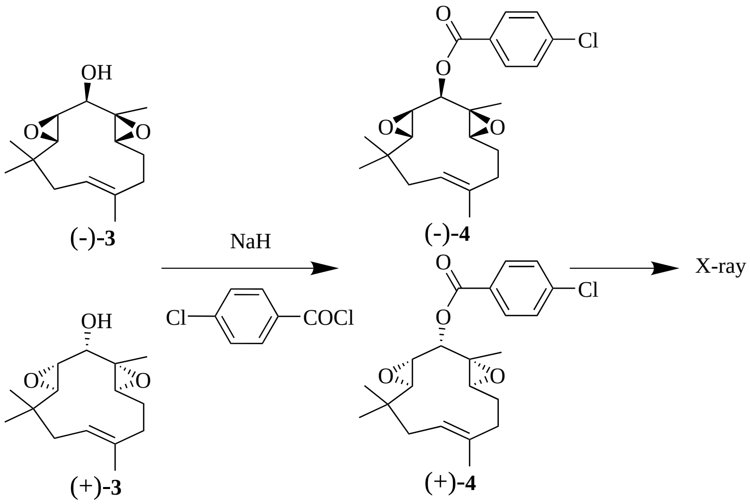
Run	DET	Reagent (equiv.)[a]	Time (h)	Yield (%)	D.e. (%)	E.e. (%)	$[\alpha]_D$
1	L	1/1.2/2	3	16	>99	>99	
2	L	1/1.2/2	7	25	>99	>99	
3	L	1/1.2/2	14	40	>99	>99	−6.5
4	L	1/1.2/2	25	40	>99	>99	−6.3
5	L	1/1.2/2	94	22	>99	91	
6	L	0.5/0.6/1	14	27	>99	>99	−6.6
7	L	5/5/5	14	40	>99	84	
8	L	1/1.2/2	14	35	>99	>99	+7.9
9	DL	1/1.2/2	14	17	>99	0	
10	–	5/0/5	28	47	>99	0	
11	–	1/0/2	14	26	>99	0	0
12	–	0/0/2	24	No reaction			
13	–	1/0/0	1	No reaction			
14	L[b]	1/1.2/2	14	10	>99	7	+0.7
15	L[c]	1/1.2/2	14	Decomposed			
16	L[d]	1/1.2/2	14	No reaction			

[a] $Ti(O\text{-}Pr^i)_4$/DET/TBHP.

[b] $VO(acac)_2$/DET/TBHP.

[c] $MoO(acac)_2$/DET/TBHP.

[d] $Al(O\text{-}Pr^i)_3$/DET/TBHP.



Scheme 2.

4. Experimental

4.1. Instruments

NMR spectra were obtained at 270 MHz for ^1H and 68 MHz for ^{13}C NMR in $CDCl_3$ with TMS as the internal standard. IR spectra were recorded on a Shimadzu 8200D. Optical rotation was measured with a JASCO DIP-181 polarimeter unless otherwise noted. Mass spectra were recorded at 70 eV, and high-resolution mass spectra (HRMS) were obtained by direct injection.

4.2. (±)-Zerumbol 2

Under an atmosphere of N_2, zerumbone **1** (1.0 g, 4.6 mmol) in absolute THF (5 mL) was added dropwise to a mixture of $LiAlH_4$ (0.70 g, 18.0 mmol) in absolute THF (5 mL), which was stirred for 3 h in an ice–salt bath. Water (50 mL) and 2 M H_2SO_4 (10 mL) were added, THF was removed on a rotary evaporator, and the mixture was extracted with EtOAc (3×30 mL). The combined organic solutions were washed with brine (3×30 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator to afford a colorless solid residue, **2** (1.0 g, 100%), mp 77.5–78.0°C, $[\alpha]_D^{23.5}=-35.4$ (EtOH, $c=0.059$). IR (KBr) 3285, 2955, 1077 cm^{-1}; ^1H NMR: δ 1.07 (s, 3H, CH_3 at C9), 1.08 (s, 3H, CH_3 at C9), 1.44 (s, 3H, CH_3 at C6), 1.67 (s, 3H, CH_3 at C2), 1.80 (dd, 1H, $J=4.95$ and 13.86 Hz, H at C8), 2.02 (dd, 1H, $J=9.90$ and 13.86 Hz, H at C8), 2.11 (m, 2H, H at C5), 2.18 (dd, 2H, $J=8.91$ and 10.56 Hz, H at C4), 4.63 (d, 1H, $J=7.26$ Hz, at C1), 4.82 (dd, 1H, $J=4.95$ and 9.90 Hz, H at C7), 5.22 (t, 1H, $J=8.91$ Hz, H at C3), 5.25 (d, 1H, $J=16.17$ Hz, H at C10), 5.56 (dd, 1H, $J=7.26$ and 16.17 Hz, H at C11); ^{13}C NMR: δ 12.72 (CH_3 at

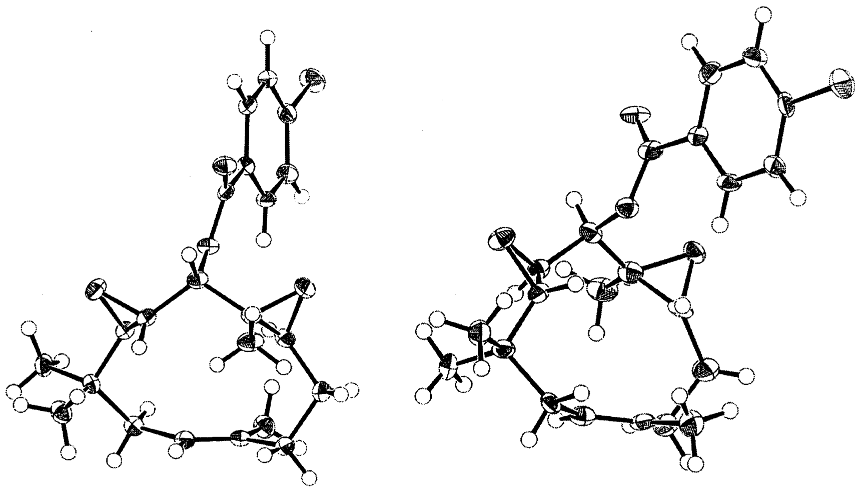

(+)-4 **(-)-4**

Figure 2. ORTEP drawing of the crystal structure of diepoxy alcohols (+)-**4** and (–)-**4**.

C2), 15.06 (CH_3 at C6), 22.95 (C4), 24.23 (CH_3 at C9), 29.42 (CH_3 at C9), 37.14 (C9), 39.18 (C5), 41.98 (C8), 78.65 (C1), 124.87 (C3), 124.91 (C7), 131.41 (C11), 133.03 (C6), 139.34 (C10), 141.85 (C2). HRMS *m*/*z* calcd mass for $C_{15}H_{24}O$ 220.1826, found 220.1828.

4.3. General procedure of Sharpless epoxidation

A mixture of Ti(OPr^i)$_4$ (644 mg, 2.27 mmol) and L-DET (560 mg, 2.72 mmol) in dry CH_2Cl_2 (20 mL) was stirred at −30°C for 10 min before adding **2** (500 mg, 2.27 mmol) and finally a solution of TBHP (5 M, 0.92 mL, 4.60 mmol). The homogeneous solution was stored in a freezer at −26°C in a reaction vessel with a serum cap. The progress of the oxidation was monitored by TLC. After 14 h the flask was placed in a −30°C bath and 10% aqueous tartaric acid (11.5 mL) was added to the solution with stirring. After 10 min the cooling bath was removed and stirring was continued at room temperature for 1 h, or until the aqueous layer became clear. The aqueous solution was extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were washed with water (30 mL) and brine (3×30 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator to leave a colorless oil whose odor indicated contamination with TBHP. The oil was taken up in ether, in an ice bath, and stirred with 1N NaOH (6.8 mL) at 0°C for 30 min. The ether layer was washed with brine (3×30 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator to leave a clear oil. Chromatography on silica gel, eluting with a 4:1 mixture of hexane and EtOAc afforded **(1*R*,2*S*,3*R*,10*S*,11*R*)-2,3-10,11-diepoxy-2,6,9,9-tetramethyl-6-cycloundecen-1-ol (–)-3** (229 mg, 40%), mp 118.0–119.0°C, $[\alpha]_D^{23.5} = -6.5$ (EtOH, *c* = 1.005). IR (KBr) 3512, 2924, 1458 cm^{-1}; ^1H NMR: δ 0.81 (s, 3H, CH_3 at C9), 1.13 (s, 3H, CH_3 at C9), 1.43 (s, 3H, CH_3 at C2), 1.43 (dddd, 1H, *J* = 3.63, 5.61, 6.26, and 9.57 Hz, H at C4), 1.67 (s, 3H, CH_3 at C6), 1.92 (d, 1H, *J* = 13.85 Hz, H at C8), 2.08 (ddd, 1H, *J* = 3.63, 3.63, and 11.22 Hz, H at C5), 2.19 (ddd, 1H, *J* = 3.63, 6.26, and 7.60 Hz, H at C5), 2.24 (dd, 1H, *J* = 9.90 and 13.85 Hz, H at C8), 2.32 (dddd, 1H, *J* = 5.28, 5.61, 7.60, and 11.22 Hz, H at C4), 2.73 (d, 1H, *J* = 2.31 Hz, H at C10), 2.82 (dd, 1H, *J* = 5.28 and 9.57 Hz, H at C3), 2.99 (t, 1H, *J* = 1.98 Hz, H at C11), 4.18 (s, 1H, H at C1), 5.14 (d, 1H, *J* = 9.90 Hz, H at C7); ^{13}C NMR: δ 15.17 (CH_3 at C6), 15.33 (CH_3 at C2), 18.87 (CH_3 at C9), 23.99 (C4), 28.38 (CH_3 at C9), 33.64 (C9), 35.92 (C5), 38.73 (C8), 55.46 (C11), 56.21 (C3), 59.30 (C10), 59.95 (C2), 68.03 (C1), 122.73 (C7), 133.55 (C6). HRMS *m*/*z* calcd mass for $C_{15}H_{24}O_3$ 252.1725, found 252.1728.

4.4. Crystallographic studies on (–)-3

A colorless prismatic crystal, 0.10×0.10×0.80 mm, orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 14.548$ (2), $b = 32.006$ (2), $c = 6.170$ (2) Å, $V = 2873.2(7)$ Å^3, $Z = 8$, $D_{calcd} = 1.167$ g/cm^3, μ(Cu Kα) = 6.35 cm^{-1} was used for data collection. The intensity data were measured on a Rigaku AFC7R diffractometer using Cu-Kα radiation at a temperature of 20.0°C by a ω–2θ scan technique. The structure was solved by direct methods (SIR92)[8] and expanded using Fourier techniques (DIRDIF94).[9] All calculations were performed using the teXsan crystallographic software package. The final cycle of full-matrix least-squares refinement was based on 1954 observed reflections ($I > 1.50\sigma(I)$) and 362 variable parameters and gave $R = 0.070$ and $R_w = 0.099$. The value of the goodness of fit indicator was 1.18.

4.5. (1*S*,2*R*,3*S*,10*R*,11*S*)-2,3-10,11-Diepoxy-2,6,9,9-tetramethyl-6-cycloundecen-1-ol (+)-3

(+)-**3** was formed in 35% yield by the same procedure; mp 125.0–125.5°C; $[\alpha]_D^{23.5} = +8.2$ (EtOH, *c* = 0.815); IR (KBr) 3516, 2922, 1456 cm^{-1}; ^1H NMR: δ 0.83 (s, 3H, CH_3 at C9), 1.12 (s, 3H, CH_3 at C9), 1.43 (dddd, 1H,

$J=3.63$, 5.61, 6.26, and 9.57 Hz, H at C4), 1.53 (s, 3H, CH_3 at C2), 1.73 (s, 3H, CH_3 at C6), 1.96 (d, 1H, $J=14.52$ Hz, H at C8), 2.12 (ddd, 1H, $J=3.63$, 3.63, and 11.22 Hz, H at C5), 2.19 (ddd, 1H, $J=3.63$, 6.26, and 7.60 Hz, H at C5), 2.24 (dd, 1H, $J=9.90$ and 13.85 Hz, H at C8), 2.32 (dddd, 1H, $J=5.28$, 5.61, 7.60, and 11.22 Hz, H at C4), 2.73 (d, 1H, $J=2.31$ Hz, H at C10), 2.82 (dd, 1H, $J=5.28$ and 9.57 Hz, H at C3), 2.99 (t, 1H, $J=1.98$ Hz, H at C11), 4.18 (s, 1H, H at C1), 5.23 (d, 1H, $J=9.90$ Hz, H at C7); ^{13}C NMR: δ 15.20 (CH_3 at C6), 15.37 (CH_3 at C2), 18.92 (CH_3 at C9), 24.03 (C4), 28.65 (CH_3 at C9), 33.68 (C9), 35.96 (C5), 38.78 (C8), 55.49 (C11), 56.26 (C3), 59.34 (C10), 59.97 (C2), 68.09 (C1), 122.79 (C7), 133.59 (C6). HRMS *m*/*z* calcd mass for $C_{15}H_{24}O_3$ 252.1725, found 252.1721.

4.6. (1*R*,2*S*,3*R*,10*S*,11*R*)-2,3-10,11-Diepoxy-2,6,9,9-tetramethyl-6-cycloundecenyl *p*-chlorobenzoate (−)-4

Under an atmosphere of N_2, (−)-**3** (300 mg, 1.20 mmol) in absolute Et_2O (5 mL) was added dropwise to a stirred suspension of sodium hydride (22.5 mg, 1.50 mmol) in absolute Et_2O (5 mL) over 10 min at room temperature. *p*-Chlorobenzoyl chloride (267 mg, 1.44 mmol) was added dropwise and the mixture was stirred for 18 h. Water (50 mL) was added and the mixture was extracted with Et_2O (3×30 mL). The combined ether solutions were washed with brine (3×30 mL), dried over Na_2SO_4, and concentrated on a rotary evaporator to afford a colorless solid residue. Chromatography on silica gel, eluting with a 6:1 mixture of hexane and EtOAc, afforded (−)-**4** (216 mg, 46%), mp 164.5–165.0°C, $[\alpha]_D^{23.5}=-18.3$ (EtOH, $c=1.010$). IR (KBr) 1720, 1595, 1275 cm^{-1}; ^1H NMR: δ 0.83 (s, 3H, CH_3 at C9), 1.12 (s, 3H, CH_3 at C9), 1.42 (dddd, 1H, $J=4.29$, 5.93, 9.24, and 10.22 Hz, H at C4), 1.52 (s, 3H, CH_3 at C2), 1.73 (s, 3H, CH_3 at C6), 1.98 (d, 1H, $J=14.52$ Hz, H at C8), 2.17 (m, 1H, H at C5), 2.21 (m, 1H, H at C5), 2.28 (dd, 1H, $J=9.90$ and 14.52 Hz, H at C8), 2.33 (dddd, 1H, $J=4.62$, 5.94, 9.24, and 9.57 Hz, H at C4), 2.62 (d, 1H, $J=2.31$ Hz, H at C10), 2.74 (dd, 1H, $J=4.29$ and 9.57 Hz, H at C3), 3.12 (t, 1H, $J=1.98$ Hz, H at C11), 5.23 (d, 1H, $J=9.90$ Hz, H at C7), 5.66 (d, 1H, $J=1.32$ Hz, H at C1), 7.40 (d, 2H, $J=8.58$ Hz, H at C3′), 7.80 (d, 2H, $J=8.58$ Hz, H at C2′); ^{13}C NMR: δ 15.38 (CH_3 at C6), 15.91 (CH_3 at C2), 18.96 (CH_3 at C9), 24.17 (C4), 28.66 (CH_3 at C9), 33.68 (C9), 35.92 (C5), 38.82 (C8), 53.59 (C11), 56.03 (C3), 58.04 (C2), 60.04 (C10), 68.91 (C1), 122.79 (C7), 128.36 (C4), 128.72 (C3'), 130.93 (C2′), 133.84 (C6), 139.41 (C1′), 164.26 (C=O). HRMS *m*/*z* calcd mass for $C_{22}H_{27}ClO_4$ 390.1598, found 390.1584.

4.7. (1*S*,2*R*,3*S*,10*R*,11*S*)-2,3-10,11-Diepoxy-2,6,9,9-tetramethyl-6-cycloundecenyl *p*-chlorobenzoate (+)-4

(+)-**4** was formed in 64% yield using the same procedure as reported for (−)-**4**; mp 156.0–157.0°C, $[\alpha]_D^{23.5}=+22.0$ (EtOH, $c=0.087$); Horiba SEPA-300); spectrums of IR (KBr), HRMS *m*/*z* calcd mass for $C_{22}H_{27}ClO_4$ 390.1598, found 390. The IR, ^1H and ^{13}C NMR spectra were identical with those of (−)-**4**.

4.8. Crystallographic studies on (−)-4

A colorless prism, 0.10×0.10×0.40 mm, trigonal, space group $P3_1$ (no. 144), $a=10.714(3)$, $c=15.4299(13)$ Å, $V=1534.0(5)$ Å^3, $Z=3$, $D_{calcd}=1.269$ g/cm^3, μ(Mo Kα) = 2.10 cm^{-1} was used for data collection. The intensity data were measured on a Rigaku Mercury detector using Mo-Kα radiation at a temperature of −180+1°C. The structure was solved by direct methods (SIR97)[10] and expanded using Fourier techniques (DIRDIF99).[11] All the calculations were performed using the CrystalStructure crystallographic software package. The final cycle of full-matrix least-squares refinement was based on 2572 observed reflections ($I>1.50\sigma(I)$) and 354 variable parameters and gave $R=0.046$ and $R_w=0.049$. The value of the goodness of fit indicator was 0.76. Flack parameter was −0.09 (12).[12]

4.9. Crystallographic studies of (+)-4

A colorless prism, 0.20×0.20×0.40 mm, trigonal, space group $P3_2$ (no. 145), $a=10.6929(5)$, $c=15.4794(4)$ Å, $V=1532.77(9)$ Å^3, $Z=3$, $D_{calcd}=1.270$ g/cm^3, μ(Mo Kα) = 2.11 cm^{-1} was used for data collection. The intensity data were measured on a Rigaku Mercury detector using Mo-Kα radiation at a temperature of −180+1°C. The structure was solved by direct methods (SIR97)[10] and expanded using Fourier techniques (DIRDIF99).[11] All calculations were performed using the CrystalStructure crystallographic software package. The final cycle of full-matrix least-squares refinement was based on 3988 observed reflections ($I>1.50\sigma(I)$) and 254 variable parameters and gave $R=0.052$ and $R_w=0.078$. The value of the goodness of fit indicator was 1.09. Flack parameter was −0.06(9).[12]

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