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Lipase-mediated resolution of octahydro-3,3,8a-trimethyl-1-naphthalenol, a key intermediate in the total synthesis of lactaranes and marasmanes

Maurice C. R. Franssen,[a,*] Hugo Jongejan,[a] Huub Kooijman,[b] Anthony L. Spek,[b,†] Roel P. L. Bell,[a] Joannes B. P. A. Wijnberg [a] and Aede de Groot [a]

[a]*Laboratory of Organic Chemistry, Wageningen University, Dreijenplein 8, 6703 HB Wageningen, The Netherlands*
[b]*Bijvoet Center for Biomolecular Research, Crystal and Structural Chemistry, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands*

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Abstract

The bicyclic alcohol (1α,8aα)-1,2,3,4,6,7,8,8a-octahydro-3,3,8a-trimethyl-1-naphthalenol (±)-**1** was resolved using *Candida rugosa* lipase-mediated esterification with vinyl acetate (*E*=72). The absolute configuration of the remaining isomer was determined by X-ray analysis of its 4-chloro-3-nitrobenzoate. The observed stereochemical preference of the enzyme is in line with the rule formulated by Kazlauskas et al. [Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem*. **1991**, *56*, 2656–2665]. The resolved alcohol is a useful chiral synthon for natural lactarane and marasmane sesquiterpenes.

1. Introduction

Sesquiterpenes possessing the lactarane and marasmane skeleton are often found in nature as metabolites of fungi belonging to the genera *Lactarius* and *Russula*.[1,2] Many of these secondary metabolites exhibit interesting physiological activities such as antifeedant, antifungal and antibacterial activity.[3–6] It is thought that these compounds take part in the mushroom's chemical defence mechanism against predators. They are formed via an enzymatic conversion of a common precursor when the mushroom is injured.[4,7,8]

In contrast to the vast number of isolated lactaranes and marasmanes, only a few total syntheses of these compounds have been described.[9–14] All of these syntheses lead to racemic products, except for

* Corresponding author. E-mail: maurice.franssen@bio.oc.wau.nl
† Address correspondence pertaining to crystallographic studies to this author. E-mail: a.l.spek@chem.uu.nl

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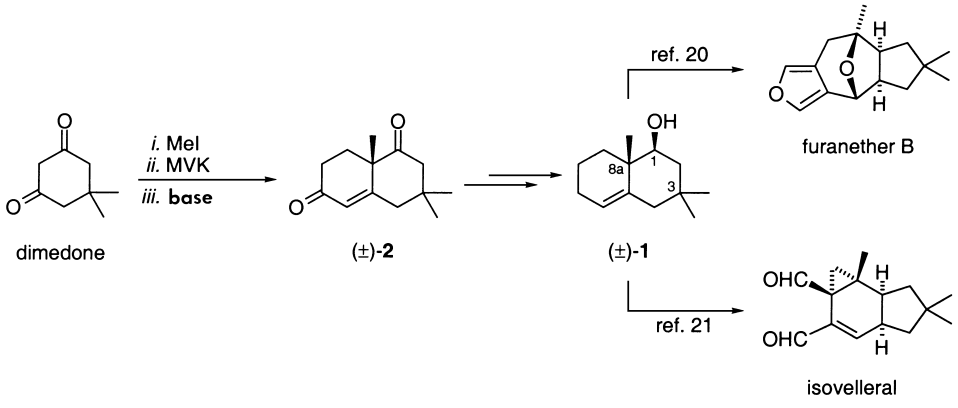
the total synthesis of the marasmane (+)-isovelleral.[11] The only known syntheses of optically active lactaranes have been achieved starting from natural congeners.[15–18]

Previously, we have demonstrated that the readily available alcohol **1**[19] is a useful building block for lactarane sesquiterpenes such as furanether B[20] (see Scheme 1). Recently, we have succeeded in converting alcohol **1** into a marasmane skeleton via a rearrangemant–cyclopropanation reaction.[21] Since we wanted to use this reaction in a new synthetic approach towards the optically active marasmane sesquiterpene isovelleral, enantiopure **1** would be required. This can, in principle, be obtained by asymmetric synthesis or enzymatic kinetic resolution. Hydrolytic enzymes such as proteases, esterases and lipases are very well suited for the kinetic resolution of racemic alcohols and esters in water or organic solvents.[22–29] However, hydrolase-mediated regio- or stereoselective conversions of decalol derivatives are relatively rare.[27–36]



Scheme 1.

In this paper, we report on the kinetic resolution of **1**, a key intermediate in the total synthesis of lactaranes[20] and marasmanes,[21] by *Candida rugosa* lipase (CRL) using vinyl acetate in diisopropyl ether. The absolute configuration of the remaining product is elucidated using X-ray analysis, and CRL's stereochemical preference for the enantiomers of **1** is discussed.

2. Results and discussion

2.1. Asymmetric synthesis

In a first attempt to prepare enantiopure **1**, we tried to synthesise its precursor dione **2** in an optically active form via an asymmetric Robinson annelation (see Scheme 1). We tested several conditions similar to the ones reported for the enantioselective synthesis of the Wieland–Miescher ketone,[37] but in all cases dione **2** was obtained as a racemate. This lack of asymmetric induction can be explained by the steric hindrance of the axial methyl group at C-3 in the transition state.[38] These negative results prompted us to investigate the enzymatic resolution of **1**.

2.2. Enzyme screening

For initial screening, **1** was incubated with 19 different esterases, lipases and proteases in the presence of a fivefold excess of vinyl acetate in octane. Very little or no reaction was observed after 6 days of incubation with 14 enzymes. The lipase B from *Candida antarctica* and lipase PS (*Pseudomonas*

Table 1
Enzymatic esterification of (±)-**1**

Enzyme[a]	solvent	acyl donor[b]	conversion (%)					
			2 h	6 h	22 h	46 h	70 h	6 d
CRL	octane	VA	14.7	20.4	23.2	23.5	23.5	23.5
CRL	octane	IPA	4.3	7.0	10.1	14.9 [c]	- [d]	-
CRL	toluene	VA	25.0	31.3	-	-	35.4	35.4
CRL	*i*Pr_2O	VA	32.3	38.8	50.0	-	-	-
CE	octane	VA	-	-	-	-	-	6.0
CVL	octane	VA	-	-	-	-	-	4.0

[a] CRL = *Candida rugosa* lipase, CE = cholesterol esterase, CVL = *Chromobacterium viscosum* lipase

[b] VA = vinyl acetate, IPA = *iso*propenyl acetate

[c] Byproducts start to appear

[d] Not determined

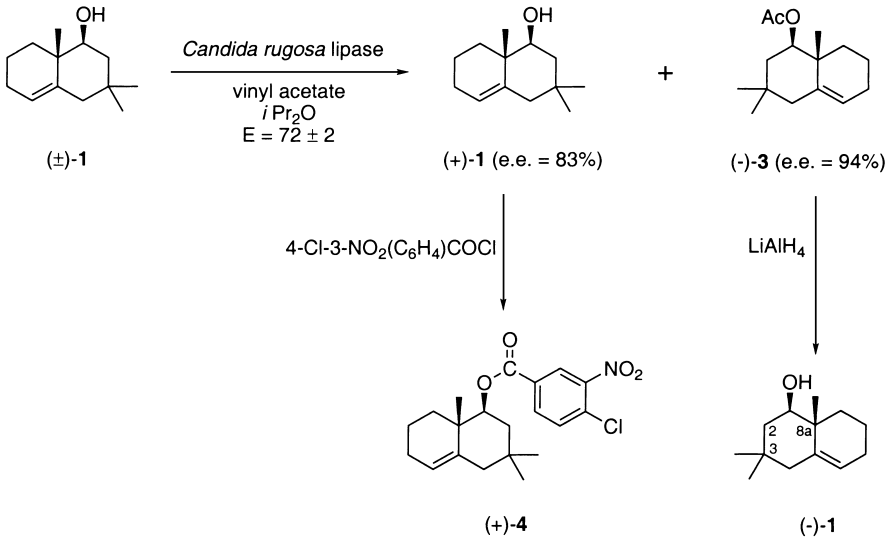
cepacia) gave, instead of the expected acetate **3**, a slow conversion into a different product, whose structure is currently under investigation. Three enzymes displayed a clean conversion of the substrate: *Candida rugosa* lipase (CRL), cholesterol esterase and *Chromobacterium viscosum* lipase (see Table 1).

Since CRL gave by far the fastest reaction, all further experiments were conducted with this enzyme. Remarkably, the enzymatic reaction in octane stopped after 22 h at only 23% conversion. Changing the acyl donor to isopropenyl acetate led to an even lower conversion. Performing the reaction in toluene improved the velocity slightly, but a much faster reaction was observed in diisopropyl ether. Incubation of **1** at 45°C for 22 h gave a 50% conversion, with an enantiomeric excess of the resulting acetate (−)-**3** of 94% (see Scheme 2). The background of this solvent effect is unknown; usually, CRL works better in apolar solvents such as octane than (log P=4.5) in more polar solvents like diisopropyl ether (log P=1.9).[22,39] Possibly, some product inhibition is taking place in the more hydrophobic solvents. Unfortunately, working in diisopropyl ether led to a decreased stability of the enzyme, since performing the esterification of **1** with reused enzyme gave a 50% reduced reaction rate. CRL-mediated hydrolysis of racemic **3** in water was relatively fast, but it was hardly stereoselective (E=~5).

Careful examination of the ee_p during various stages of the CRL-mediated esterification of **1** with vinyl acetate in diisopropyl ether allowed an accurate determination of the E-value,[40] which proved to be 72±2%. The remaining alcohol (+)-**1** was obtained in 83% ee, the acetate (−)-**3** in 94% ee. The ee of (−)-**1** could be enhanced to >98% by performing the kinetic resolution a second time. Reduction of (−)-**3** with $LiAlH_4$ gave alcohol (−)-**1**. In this way, the kinetic resolution of **1** was easily accomplished, yielding both enantiomers with high enantiomeric excess.

2.3. Determination of the absolute configuration of (+)-1

Since no enantiomerically pure reference material of **1** or any derivative was available, the only way to determine the absolute configuration of the enzymatic product was by X-ray analysis of a crystalline



Scheme 2.

derivative. Several attempts to prepare suitable crystalline derivatives were unsuccessful. Esterification of (+)-**1** with 3,4,5-triiodobenzoyl chloride, a method which was very successful in a previous study,[22] gave several unidentified compounds in this case. The racemic 4-bromobenzoyl derivative of **1** was easily obtained as a high-melting solid, but the corresponding optically active material was not crystalline. Treatment of (+)-**1** with 4-chloro-3,5-dinitrobenzoyl chloride gave decomposition products. Finally, suitable crystals were obtained from the reaction of (+)-**1** with 4-chloro-3-nitrobenzoyl chloride in DMAP/pyridine.

The crystal structure of the ester **4** was determined. The molecular structure is shown in Fig. 1. The absolute configuration was established based on anomalous dispersion; details are given in Section 4.8. The molecule displays the *S* configuration at both positions 1 [atom C(1)] and 8a [atom C(10)]. A second crystal from the same batch displayed the same absolute configuration on positions 1 and 8a.

The six-membered ring containing C(1) adopts a chair conformation; the ring containing C(6) is in a half-chair conformation, with C(8) and C(9) out of the plane. The orientation of the chloro-nitrophenyl moiety with respect to the octahydronaphthalene is best characterized by the torsion angle C(10)–C(1)–O(1)–C(14), which amounts to −159.9(2)°.

2.4. CRL's stereochemical preference for secondary alcohols

A rule for the stereochemical preference of CRL towards linear and cyclic alcohols has been formulated by Kazlauskas et al.[42] (**5**, see Fig. 2). Compound **6**[43] was the only hydronaphthol isostere which was included in these studies. When the preferred enantiomer of our substrate [(−)-**1**, see Scheme 2] is compared to the rule, it appears that the nearby axial methyl group on C8a plays a much more important role than the methyl groups on C3, making the bridgehead carbon the 'large' substituent and C2–C3 the 'medium-sized' group. This is not trivial, since Kazlauskas' rule is based on monocyclic or small bicylic secondary alcohols. As substrates become larger and more substituted, there may be a point where the rule no longer applies.

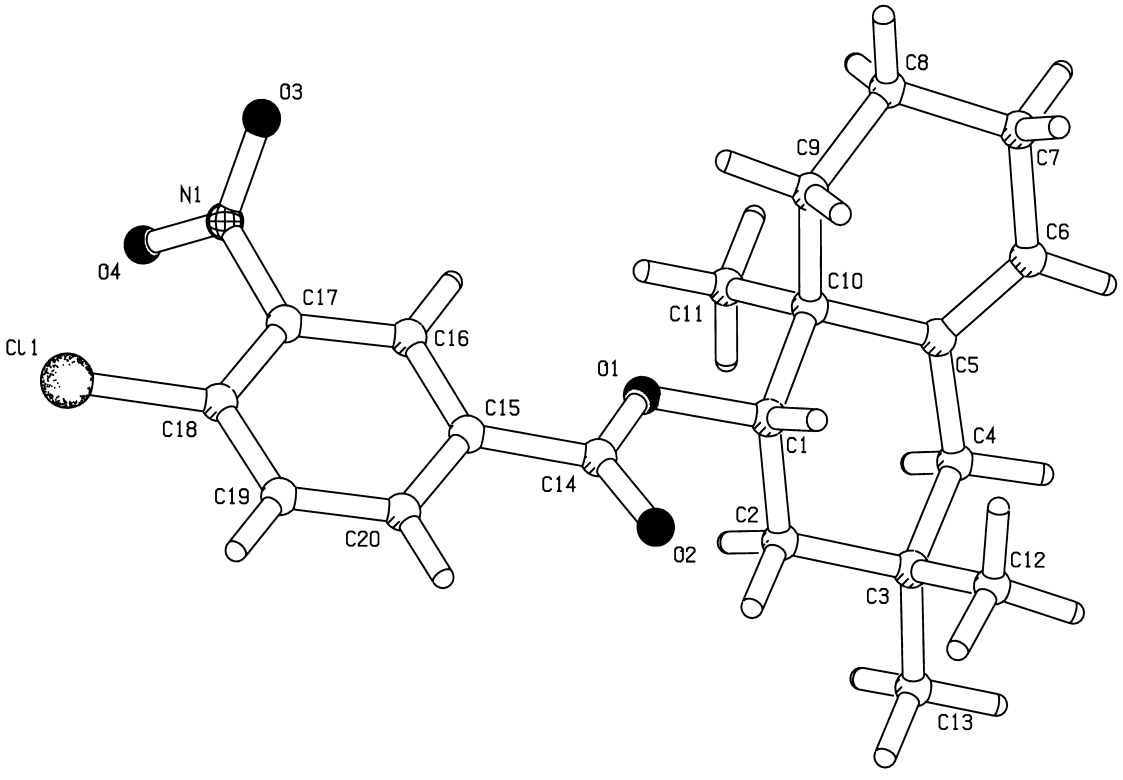
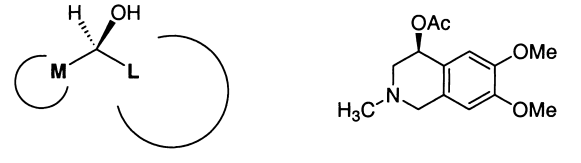


Figure 1. PLUTON[41] plot of **4** with the adopted numbering scheme



5
M = medium-sized group
L = large group

6
(resolved using CRL;
preferred enantiomer shown)

Figure 2.

3. Conclusions

We were able to show that octahydro-3,3,8a-trimethyl-1-naphthalenol **1** can be resolved using *Candida rugosa* lipase, giving the enantiomers (+)-**1** and (−)-**3** in 83% and 95% ee, respectively (*E*=72). The ee of (+)-**1** can be increased to >98% by performing the kinetic resolution once more. The absolute configuration of the remaining substrate (+)-**1** was established by X-ray analysis of its 4-chloro-3-nitrobenzoate **4**. The observed stereochemical preference of CRL during this kinetic resolution was in line with Kazlauskas' rule. The enzymatic resolution of this chiral building block allows the preparation of both enantiomers of lactaranes and marasmanes, which may be useful for structure–activity studies.

4. Experimental

4.1. Enzymes and chemicals

Candida rugosa lipase (type VII), porcine pancreas lipase, thermolysin and subtilisin Carlsberg were from Sigma; α-chymotrypsin, *Rhizomucor miehei* lipase (Chirazyme L-9, lyo.) and *Candida antarctica* lipase (Chirazyme L-2 lyo.) were from Boehringer; cholesterol esterase, lipase PS (*Pseudomonas cepacia*), lipase AP6 (*Aspergillus* sp.), lipase N (*Rhizopus* sp.), lipase R-10 (*Penicillium roqueforti*), protease P6 (*Aspergillus melleus*) and acylase 30,000 (*Aspergillus* sp.) were from Amano; *Chromobacterium viscosum* lipase, *Aspergillus niger* lipase and *Geotrichum candidum* lipase were from Biocatalysts Ltd; *Humicola lanuginosa* lipase (SP 523) was from Novo Nordisk.

3-Nitro-4-chlorobenzoylchloride and vinyl acetate were obtained from Acros. 4-Bromobenzoyl chloride was prepared from 4-bromobenzoic acid (Janssen Chimica). (±)-(1α,8aα)-1,2,3,4,6,7,8,8a-Octahydro-3,3,8a-trimethyl-1-naphthalenol **1** was synthesised according to Orru et al.[19] All solvents were distilled before use.

4.2. Apparatus and analytical techniques

^{1}H NMR spectra were determined on a Bruker AC-E 200 machine. Chemical shifts are reported in ppm downfield relative to tetramethylsilane in $CDCl_3$ solutions. Tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) was used as a shift reagent for CLIS-NMR. Mass spectral data and HRMS measurements were obtained on a Finnigan Mat 95 and on an HP 5973 MSD. Elemental analyses were carried out using a Carlo Erba Elemental Analyzer 1106. Optical rotations were measured on a Perkin–Elmer 241 polarimeter in $CHCl_3$ as the solvent with the concentrations denoted in units of g/100 ml. The enzymatic reactions were carried out at 45°C in a New Brunswick Scientific G24 Environmental Incubator Shaker at 350 rpm.

GC analysis and measurements to determine the enantiomeric excess (ee) were carried out with a Varian 3600 gas chromatograph provided with a Lab Systems X-Chrom integrating system and a 50 m capillary WCOT fused silica column filled with CP-cyclodextrin B-236-M-19, film thickness 0.25 μm, using a temperature programme of 80–170°C, rate 2°C/min, FID and H_2 as carrier gas. Tetradecane was used as an internal standard. The acetates (−)-**3** and (+)-**3** were baseline separated by this method, but the peaks of the enantiomers of alcohol **1** showed considerable overlap. In order to separate the alcohols, samples of the enzymatic reaction mixture were silylated using trimethylsilyl chloride and hexamethyldisilazane.[44] A GC oven temperature of 90°C was used for this purpose. The *E* value could be determined most accurately from the ee_p and the conversion, at an oven temperature of 90°C, using the computer programme SIMFIT.[45]

4.3. Enzyme screening

In a 4 ml screw cap vial (Chrompack) was placed 1 ml of a solution containing 100 mM of (±)-**1** and 500 mM of vinyl acetate (freshly distilled) in octane. A suitable amount of enzyme (5–100 mg, depending on the purity) was added to the prewarmed solution and the mixture was incubated at 45°C. At regular time intervals, samples were analysed by GC in order to monitor the conversion and ee. Very slow or no reaction was observed with porcine pancreas lipase, *Rhizomucor miehei* lipase, lipase AP6 (*Aspergillus* sp.), lipase N (*Rhizopus* sp.), lipase R-10 (*Penicllium roqueforti*), *Aspergillus niger* lipase, *Geotrichum candidum* lipase, lipoprotein lipase from two microbial sources, α-chymotrypsin,

thermolysin, subtilisin Carlsberg, protease P6 (*Aspergillus melleus*) and acylase 30,000 (*Aspergillus* sp.). Blank reactions containing (±)-**1** and vinyl acetate in octane without enzyme showed no conversion.

*4.4. (1*R*,8a*R*)-1,2,3,4,6,7,8,8a-Octahydro-3,3,8a-trimethyl-1-naphthalenol acetate (−)-**3** and (1*S*,8a*S*)-1,2,3,4,6,7,8,8a-octahydro-3,3,8a-trimethyl-1-naphthalenol (+)-**1***

To a solution of 1.94 g (10 mmol) of (±)-**1** and 4.30 g (50 mmol) of freshly distilled vinyl acetate in 45 ml of diisopropyl ether, 7.5 g of *Candida rugosa* lipase was added. The mixture was shaken at 45°C for 22 h after which the enzyme was filtered off. The filtrate was dried over $MgSO_4$, filtered and evaporated in vacuo till dryness. The resulting mixture was separated by column chromatography (silica gel, eluent hexane:ethyl acetate=9:1) yielding 0.81 g of (−)-**3** (34%, 94% ee) and 1.04 g of (+)-**1** (54%, 83% ee), R_f values: 0.50 and 0.31, respectively. ^{1}H NMR [(−)-**3**]: δ 0.82 (s, 3H), 0.89 (s, 3H), 0.99 (s, 3H), 1.20–2.20 (m, 10H), 1.96 (s, 3H), 4.69 (m, 1H), 5.34 (m, 1H). HRMS theor. (M^+): 236.1776; found: 236.1778. $[\alpha]_D^{20}$=−48.0 (*c* 2.2). ^{1}H NMR [(+)-**1**]: δ 0.82 (s, 3H), 0.95 (s, 3H), 0.98 (s, 3H), 1.34–2.20 (m, 10H), 3.48 (m, 1H), 5.38 (m, 1H). The remaining alcohol was once more incubated with CRL under the conditions described above, yielding (+)-**1** with >98% ee: $[\alpha]_D^{20}$=+69.0 (*c* 2.9).

*4.5. Reduction of (−)-**3** into (−)-**1***

To a suspension of 0.102 g (2.7 mmol) of $LiAlH_4$ into 25 ml of dry ether, a solution of 0.524 g (2.2 mmol) of (−)-**3** in 25 ml of dry ether was added over a period of 20 min. After stirring for another 20 min the reaction was quenched by careful addition of 10 ml of 1 M hydrochloric acid to the reaction mixture. After the organic layer was separated, the water layer was extracted with 2×25 ml of ether. The organic extracts were washed twice with brine, dried over $MgSO_4$, filtered and evaporated in vacuo yielding 0.431 g of a solid which was purified by column chromatography (silica gel, eluent hexane:ethyl acetate, 9:1), to afford 0.421 g (98%) of (−)-**1** (95% ee), $[\alpha]_D^{20}$=−67.4 (*c* 12.2).

*4.6. (1α,8aα)-1,2,3,4,6,7,8,8a-Octahydro-3,3,8a-trimethyl-1-naphthalenol 4-bromobenzoate **7***

This ester was prepared as described below for **4**, using 0.097 g (0.5 mmol) of (+)-**1** (83% ee), 0.216 g (1.0 mmol) of *p*-bromobenzoyl chloride and 0.061 g (0.5 mmol) of DMAP in 2 ml of pyridine, yielding 250 mg of the crude product which was purified by column chromatography (silica gel, eluent hexane:ethyl acetate, 9:1). The obtained product (135 mg, R_f value: 0.9 with the same solvent as the eluent) consisted of crystals of a racemic mixture of **7** (30 mg, recrystallized from methanol, m.p.: 97°C) and 80 mg of an oil of (−)-**7** (>95% ee, determined by CLIS-NMR). ^{1}H NMR [(−)-**7**]: δ 0.92 (s, 3H), 0.97 (s, 3H), 1.18 (s, 3H), 1.30–2.20 (m, 10H), 4.93 (t, *J*=8.3 Hz, 1H), 5.44 (m, 1H), 7.55 (d, *J*=8.4 Hz, 2H), 7.86 (d, *J*=8.4 Hz, 2H). HRMS theor. (M^+): 376.1038; found: 376.1039. $[\alpha]_D^{20}$=−93.45 (*c* 3.65). Anal. calcd for $C_{20}H_{25}BrO_2$: C, 63.66%; H, 6.68%; found: C, 63.28%; H, 6.68%.

*4.7. (1*S*,8a*S*)-1,2,3,4,6,7,8,8a-Octahydro-3,3,8a-trimethyl-1-naphthalenol 4-chloro-3-nitrobenzoate **4***

To a solution of 0.194 g (1.0 mmol) of (+)-**1** (83% ee) and 0.122 g (1.0 mmol) of DMAP in 5 ml of pyridine was added 0.438 g (2.0 mmol) of 4-chloro-3-nitrobenzoyl chloride. The reaction mixture was refluxed for 3 h. After cooling to room temperature, the reaction mixture was poured into 20 ml of water, brought to pH 4 with conc. H_2SO_4 and extracted four times with 10 ml portions of methylene chloride. The combined extracts were dried over $MgSO_4$, filtered and evaporated in vacuo till dryness,

yielding 400 mg of crude product which slowly solidified upon standing. The solid was purified by column chromatography (silica gel, eluent hexane:ethyl acetate, 8:2) giving 220 mg of an oil which partly crystallised after addition of 2 ml of hexane yielding 70 mg of crystals of a racemic mixture of **4** and *ent*-**4**, m.p.: 92–94°C. The mother liquor was decanted, evaporated till dryness and the residual solid (110 mg) was recrystallised from methanol yielding 90 mg of **4** [>95% ee, determined by CLIS-NMR, m.p.: 61–64°C, $[\alpha]_D^{20}$=+92.0 (*c* 2.2)] which was used for X-ray diffraction analysis. ^{1}H NMR (**4**): δ 0.93 (s, 3H), 0.98 (s, 3H), 1.18 (s, 3H), 1.40–2.20 (m, 10H), 5.00 (m, 1H), 5.45 (m, 1H), 7.62 (d, *J*=8.4 Hz, 1H), 8.11 (dd, *J*=2.0 Hz and 8.4 Hz, 1H), 8.43 (d, *J*=2.0 Hz, 1H). HRMS theor. (M^+): 377.1394; found: 377.1402. Anal. calcd for $C_{20}H_{24}ClNO_4$: C, 63.57%; H, 6.40%; N, 3.71%; found: C, 63.28%; H, 6.45%; N, 3.28%.

*4.8. Crystal structure determination of **4***

A colourless, block-shaped crystal (0.15×0.30×0.30 mm) was glued to the tip of a glass fibre and transferred into the cold nitrogen stream on an Enraf–Nonius CAD4-T diffractometer on rotating anode. Accurate unit-cell parameters and an orientation matrix were determined by least-squares fitting of the setting angles of 25 well-centred reflections (SET4)[46] in the range 9.93°<θ<13.96°. The crystals of **4** are monoclinic, space group $P2_1$ (no. 4) with *a*=7.5638(7), *b*=6.7267(8), *c*=18.921(2) Å, β=98.398(8)°, *V*=952.37(18) Å^3, M_r=377.87, *Z*=2, D_x=1.318 g cm^{-3}, *F*(000)=400 e, μ(MoKα)=0.23 mm^{-1}. Reduced-cell calculations did not indicate higher lattice symmetry.[47] Data were collected at 150 K in ω scan mode with scan angle Δω=0.68+0.35tan θ°. Intensity data of 6356 reflections were collected in the range 1.1°<θ<27.5°, −9≤*h*≤9, −8≤*k*≤8, −24≤*l*≤24. Averaging of symmetry equivalent reflections (R_{int}=0.0412) gave 4364 independent reflections, 3988 of which were Friedel-related. Data were corrected for *Lp* effects and for a linear instability of 10% of the three periodically measured reference reflections (2 1 6, 2 2 3, 1 3 2) during 25 h of X-ray exposure time. Absorption correction was not carried out. The structure was solved by automated direct methods and subsequent difference Fourier technique (SHELXS86).[48] Refinement on F^2 was carried out by full-matrix least-squares techniques (SHELXL-97-2).[49] No observance criterion was applied during refinement. Hydrogen atoms were included in the refinement on calculated positions riding on their carrier atoms. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were refined with a fixed isotropic thermal parameter related to the value of the equivalent isotropic displacement parameter of their carrier atoms by a factor of 1.5 for the methyl hydrogen atoms, and a factor of 1.2 for the other hydrogen atoms. Refinement of 238 parameters converged at a final w*R*2 value of 0.1104, *R*1=0.0475 [for 3478 reflections with $I>2\sigma(I)$] and *S*=1.041, where $wR2=[\Sigma[w(F_{o2}-F_{c2})^2]/\Sigma[w(F_{o2})^2]]^{1/2}$, $w=1/[\sigma^2(F^2)+(0.0392P)^2+0.37P]$ $P=(\max(F_{o2},0)+2F_{c2})/3$, and $R1=\Sigma||F_o|-|F_c||/\Sigma|F_o|$. All difference Fourier peaks lie within the range −0.23<Δρ<0.34 e Å^{-3}.

Refinement of a racemic twin model resulted in a twin ratio *S,S*:*R,R* of 1.00(9):0.00. Based on this result the twin model was abandoned and only the *S,S* configuration was included in the final refinement. The Flack *x* parameter, calculated during the final structure factor evaluation of this model, amounted to a value of −0.13(8). Refinement of the *R,R* configuration resulted in a w*R*2-value of 0.1368, *R*1=0.0499, while the *x* parameter was calculated to be 1.11(9).

Neutral atom scattering factors and anomalous dispersion corrections were taken from the *International Tables for Crystallography*.[50] Geometrical calculations and illustrations were performed with PLATON[51] and PLUTON.[41] All calculations were performed on a DEC Alpha work station.

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