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(*R*)-(+)-[VCD(–)984]-4-Ethyl-4-methyloctane: A Cryptochiral Hydrocarbon with a Quaternary Chiral Center. (1) Synthesis of the Enantiopure Compound and Unambiguous Determination of Absolute Configuration

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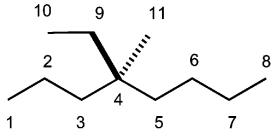
Enantiopure (*R*)-(+)-[VCD(–)984]-4-ethyl-4-methyloctane (**1**), a cryptochiral hydrocarbon with a quaternary chiral center, was synthesized by the use of 2-methoxy-2-(1-naphthyl)propionate (MαNP) and (–)-camphorsultam dichlorophthalic (CSDP) acid methods. The diastereomeric MαNP and CSDP acid esters prepared from racemic 2-butyl-2-methyl-1-tetralols, were effectively separated by HPLC on silica gel, and their absolute configurations were unambiguously determined by X-ray crystallographic analysis and ^{1}H NMR anisotropy methods. The recovered enantiopure 2-butyl-2-methyl-1-tetralol [(1*S*,2*S*)-(+)-*cis*-**9**] was then converted into the hydrocarbon (+)-**1**, the *R* absolute configuration of which was unambiguously determined for the first time. The structure of hydrocarbon **1** was also confirmed by NMR HSQC-TOCSY analysis.

Introduction

The science of stereochemistry started when L. Pasteur first succeeded in the so-called "optical resolution" of racemic tartaric acid in 1848, and then the theory of "tetrahedral carbon atom" was proposed independently by J. H. van't Hoff and J. A. Le Bel in 1874 to explain the enantiomeric structures of optically active compounds. Compounds having a tetrahedral carbon atom substituted with four different groups represent the fundamental structure of molecular chirality. 4-Ethyl-4-methyloctane (**1**) is one such fundamental chiral molecule; it contains a simple chiral saturated hydrocarbon with a quaternary chiral center, to which four different, unbranched alkyl groups (methyl, ethyl, propyl, and butyl groups), are bonded (Figure 1). Unlike chiral compounds with functional groups, compound **1** is an alkane without any polarizable group, and all four alkyl groups are similar to each other. Therefore, its optical rotation would be extremely small, falling in the category of so-called cryptochirality.[1]



(*R*)-(+)-[VCD(–)984]-**1**

enantiopure (*R*)-(+)-**1**,
$[\alpha]_D^{25}$ = +0.19 (neat, ρ = 0.7565);
$[\alpha]_{365}^{23}$ = +0.70 (neat, ρ = 0.7565)

Figure 1. Absolute configuration of 4-ethyl-4-methyloctane **1** determined in this study.

In 1980, H. Wynberg and a co-worker first reported the synthesis of both enantiomers (–)-**1** (95% *ee*) and (+)-**1** (85% *ee*), which showed small specific rotations, $[\alpha]_{578}$ = –0.198 and $[\alpha]_{578}$ = +0.185 (neat), respectively (Scheme 1); in this approach, menthyl ester **2** was resolved by recrystallization, and carboxylic acid **3** was resolved with cinchonidine.[2] It was thus difficult to obtain the synthetic precursors of hydrocarbon **1** in an enantiopure form by recrystallization. In addition, the absolute configuration of **1** remained undetermined. In 1988, L. Lardicci and co-workers reported the synthesis and absolute configurational assignment of (+)-**1**,[3] where acetylene *tert*-alcohol **4** was resolved as its phthalate half-ester/brucine salt, and then the recovered chiral alcohol **4** was converted into hydrocarbon (+)-**1** through bromo-allene **6** (Scheme 1). However, although the absolute configuration of acetylene *tert*-alcohol **4** was determined by applying the CD exciton chirality method[4] to its benzoate **5**, the observed CD (λ_{ext} = 230 nm, $\Delta\varepsilon$ = +0.8)[3] is too small to make a clear assignment. Therefore, it remains an intriguing challenge to synthesize enantiopure hydrocarbon **1** with cryptochirality and to determine its ab-

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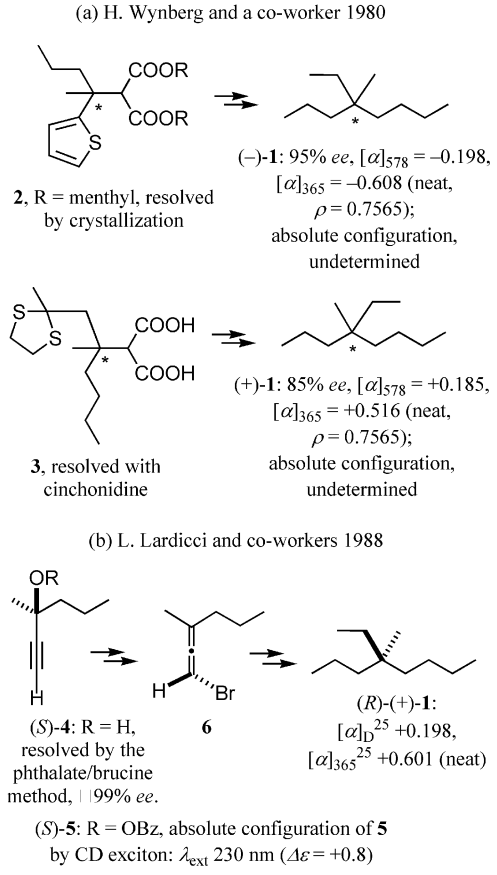
solute configuration in an unambiguous manner.[5] We report here, in Part 1 of a two-part paper, the synthesis of enantiopure (+)-**1** and make the first unambiguous absolute configurational assignment by ^{1}H NMR anisotropy and by X-ray crystallographic analysis.[6] In the following paper, Part 2, the vibrational circular dichroism (VCD)[7] characterization of hydrocarbon [VCD(–)984]-**1** and the independent absolute configurational assignment by ab inito calculation of the VCD spectra will be discussed.



Scheme 1. Syntheses of chiral hydrocarbon **1** previously reported.

Recently, we have developed the (–)-camphorsultam dichlorophthalic (CSDP) ester method[8] using CSDP acid (Figure 2), which is very useful for the enantioresolution of racemic aromatic alcohols and determination of their absolute configurations by X-ray crystallographic analysis. In this approach, the racemic alcohol is esterified with enantiopure (–)-CSDP acid, yielding diastereomeric esters, which are separated well by HPLC on silica gel. If the diastereomeric CSDP esters are base-line-separated by HPLC, the separated esters are guaranteed to be enantiopure. This is an advantage of the CSDP acid method by using HPLC, compared to resolution by recrystallization. Some CSDP esters are obtained as single crystals that are suitable for X-ray crystallographic analysis and, therefore, its absolute configuration can be unambiguously determined by reference to the CSDP acid moiety as an internal reference. The enantiopure alcohol with established absolute configuration could be subsequently recovered by hydrolysis.[8]

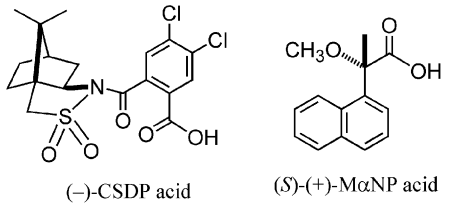


Figure 2. Chiral acids used for the enantioresolution of racemic alcohols and the determination of absolute configurations.

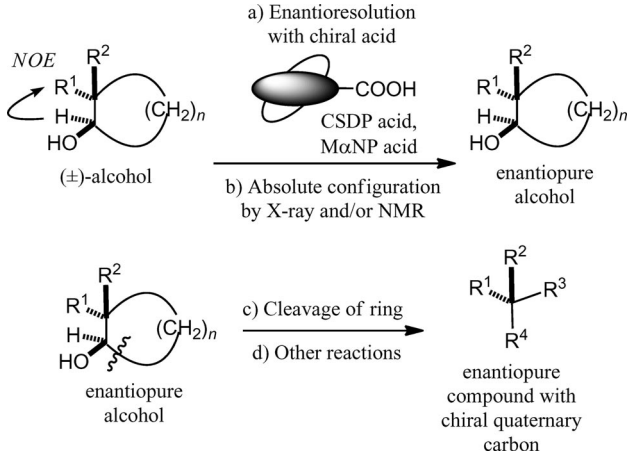
The CSDP acid method is thus useful for enantioresolution and absolute configurational assignment. However, it is not always possible to obtain single crystals suitable for X-ray crystallographic analysis. If X-ray analysis is not possible, the absolute configuration cannot be determined. For such cases, we have recently developed the 2-methoxy-2-(1-naphthyl)propionate (MαNP) ester method[8b–8f,9] using chiral MαNP acid (Figure 2) as an alternative, which is very powerful for enantioresolution of racemic alcohols, especially aliphatic alcohols, and simultaneous determination of their absolute configurations by ^{1}H NMR anisotropy. The method has been successfully applied to various alcohols.[8b–8f,9] In this approach, racemic alcohol is esterified with enantiopure (*S*)-(+)-MαNP acid, yielding diastereomeric esters that can be effectively separated by HPLC on silica gel. The application of the ^{1}H NMR anisotropy method to the separated, enantiopure, diastereomeric MαNP esters leads to the absolute configurational assignment of the alcohol moiety. Single crystals are thus unnecessary for this method and, therefore, it is applicable to most secondary alcohols. Although the ^{1}H NMR anisotropy method is an empirical rule, we have never encountered any exception, which is a great advantage of the MαNP ester method. The solvolysis of the separated MαNP ester yields the enantiopure alcohol with an established absolute configuration.[8b–8f,9]

Although the MαNP/^{1}H NMR anisotropy method does not require crystallization, MαNP esters can sometimes be obtained as single crystals, which can be subjected to X-ray crystallographic analysis.[9f] In these cases, the absolute configuration of the alcohol part can be unambiguously determined, because the absolute configuration of the MαNP acid part is known. The absolute configuration of the MαNP ester can thus be doubly determined by both ^{1}H NMR anisotropy and X-ray crystallographic methods. We have never experienced any exceptional case showing a disagreement between these NMR and X-ray methods.[9f] These CSDP acid and MαNP acid methods were applied to the synthesis of enantiopure hydrocarbon **1** to unambiguously determine its absolute configuration as described below.

Results and Discussion

Synthetic Strategy and Absolute Configurational Assignment

We adopted the synthetic strategy and absolute configurational assignment as shown in Scheme 2, in an approach that is generally applicable to acyclic chiral compounds with a quaternary chiral center.

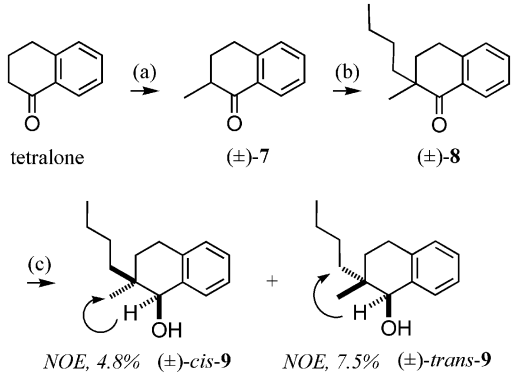


Scheme 2. General synthetic strategy for acyclic chiral compounds with a quaternary chiral center and their absolute configurational assignment.

As a starting material, a racemic cyclic secondary alcohol was chosen in which the relative stereochemistry of groups R^1 and R^2 could be determined by NOE experiments. The racemic alcohol can be enantioresolved as the CSDP ester and/or the MαNP ester as described above, and their absolute configurations can be determined by ^{1}H NMR anisotropy and/or X-ray crystallographic analysis. The recovered enantiopure alcohol can then be subjected to a ring-opening reaction and then converted into the desired acyclic compound with a quaternary chiral center. The reason we selected the cyclic alcohol as a starting material is as follows. Even if single crystals of CSDP ester or MαNP ester could not be obtained, the relative configuration could still be determined by NOE experiments, and the absolute configuration by ^{1}H NMR anisotropy. In this strategy, the chirality of the quaternary stereogenic center is always kept unchanged and, therefore, the synthetic reactions lead to unambiguous absolute configurational assignment of the target compound.

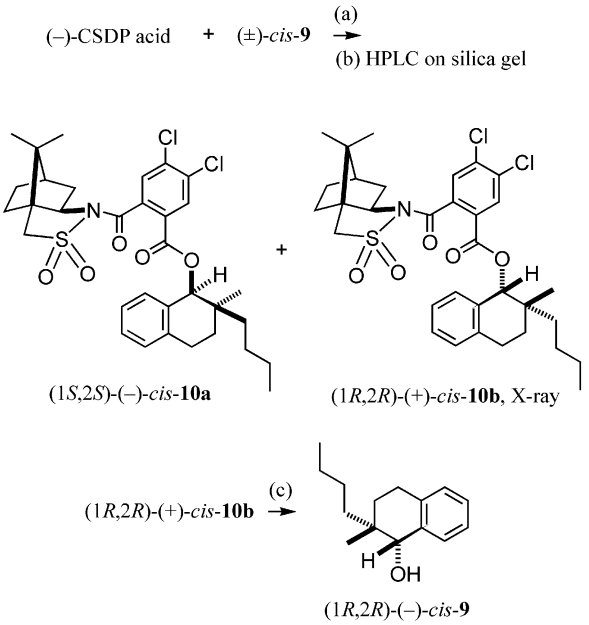
Application of the CSDP Acid Method

Tetralone was converted into 2-methyltetralone (**7**) by a modification of the reported procedure,[10] and then into 2-butyl-2-methyl-1-tetralone (**8**), which was reduced with $LiAlH_4$ yielding *cis*-2-butyl-2-methyl-1-tetralol (**9**; 69%) and *trans*-alcohol (**9**; 31%) (Scheme 3). The relative configuration of *cis*-**9** was determined by observation of an NOE (4.8%) correlation between the 2-methyl group and the 1-methine proton. The configuration of *trans*-**9** was similarly determined by the observation of an NOE (7.5%) correlation between the methylene protons of 2-butyl group and the 1-methine proton, as shown in Scheme 3.



Scheme 3. Preparation of racemic 2-butyl-2-methyl-1-tetralols: (a) LDA, THF, HMPA, –78 °C, then MeI, –40 °C (88%). (b) *t*BuOK, THF, reflux, then BuI (72%). (c) $LiAlH_4$, THF (69% for *cis*-**9**, 31% for *trans*-**9**).

The major alcohol (±)-*cis*-**9** was esterified with (–)-CSDP acid to give the diastereomeric esters, which separated well by HPLC on silica gel (hexane/EtOAc, 6:1; separation factor α = 1.17; resolution factor R_s = 1.51), affording the first-eluted CSDP ester (–)-*cis*-**10a** (yield 50%) and the second-eluted CSDP ester (+)-*cis*-**10b** (47%) (Scheme 4). It should be noted that the two diastereoisomeric CSDP esters **10a/10b** were base-line-separated, as shown in Figure 3 (a) and, hence, the separated esters were enantiopure.



Scheme 4. Preparation of CSDP esters of *cis*-alcohol (±)-**9**, HPLC separation, and recovery of enantiopure alcohol (1*R*,2*R*)-(–)-*cis*-**9**: (a) DCC, DMAP, CH_2Cl_2. (b) HPLC on silica gel (hexane/EtOAc, 6:1), yield (1*S*,2*S*)-(–)-*cis*-**10a**, 50%, and (1*R*,2*R*)-(+)-*cis*-**10b**, 47%. (c) KOH, MeOH (88%).

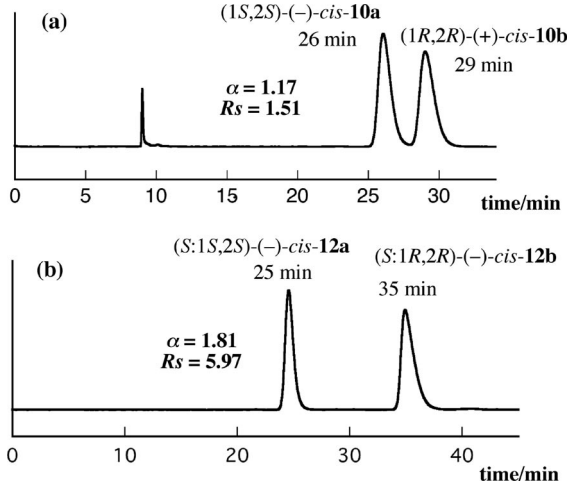


Figure 3. HPLC separation of diastereomeric esters on silica gel (22 × 300 mm): theoretical plate number N = 9300–10800; detector: UV, 254 nm; flow rate: 10 mL/min; α = separation factor; R_s = resolution factor. (a) CSDP esters (1*S*,2*S*)-(–)-*cis*-**10a** and (1*R*,2*R*)-(+)-*cis*-**10b**: sample injected, 10 mg; hexane/EtOAc, 6:1. (b) MαNP esters (*S*:1*S*,2*S*)-(–)-*cis*-**12a** and (*S*:1*R*,2*R*)-(–)-*cis*-**12b**: sample injected 25 mg; hexane/EtOAc, 15:1.

When CSDP ester (+)-*cis*-**10b** was recrystallized from $EtOH/CH_2Cl_2$, single crystals were obtained as expected, and subjected to X-ray analysis [orthorhombic, $P2_12_12_1$ (#19); R/R_w = 0.0598/0.0740; R/R_w for the mirror image = 0.0719/0.0899].

From the X-ray crystal structure of (+)-*cis*-**10b** shown in Figure 4 (a), the relative configuration was clearly determined to be *cis*, confirming the NOE assignment. The absolute configuration of (+)-*cis*-**10b** was also unambiguously determined to be (1*R*,2*R*) by reference to the absolute configuration of the CSDP acid moiety. In addition, the (1*R*,2*R*) absolute configuration was confirmed by the anomalous dispersion effect of the chlorine and sulfur atoms, as indicated above. The CSDP ester (+)-*cis*-**10b** was easily hydrolyzed to yield the enantiopure alcohol (1*R*,2*R*)-(–)-*cis*-**9**.

Racemic *trans*-alcohol (±)-*trans*-**9** was similarly esterified with (–)-CSDP acid, giving diastereomeric esters that were also separated by HPLC on silica gel (hexane/EtOAc, 6:1; separation factor α = 1.12; resolution factor R_s = 1.10) affording the first-eluted CSDP ester (–)-*trans*-**11a** (50%) and the second-eluted CSDP ester (+)-*trans*-**11b** (50%) (Scheme 5). Compared to the *cis*-CSDP esters **10a/10b**, the HPLC separation of **11a/11b** was less effective, as indicated by the separation factor α = 1.12; however, pure esters were obtained by repeated HPLC separation. Although both CSDP esters **11a** and **11b** were obtained as colorless solids, no single crystals suitable for X-ray crystallographic analysis could be obtained. Therefore, at this point, the absolute configurations of the alcohol moieties in CSDP esters **11a** and **11b** could not be determined (they were later unambiguously determined as shown in Scheme 5 by chemical correlation as discussed below). From the second-eluted ester (+)-*trans*-**11b**, enantiopure alcohol (1*R*,2*S*)-(–)-*trans*-**9** was recovered.

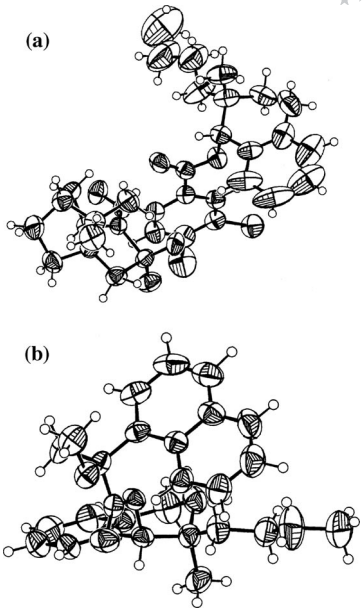
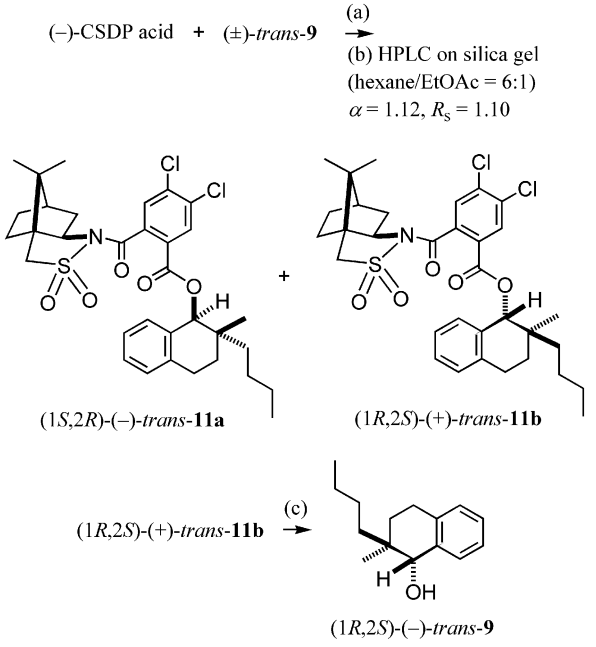


Figure 4. X-ray crystal structure establishing the absolute configuration: (a) CSDP ester (1*R*,2*R*)-(+)-*cis*-**10b**; (b) MαNP ester (*S*:1*R*,2*R*)-(–)-*cis*-**12b** taken from S. Kuwahara et al.[9f]

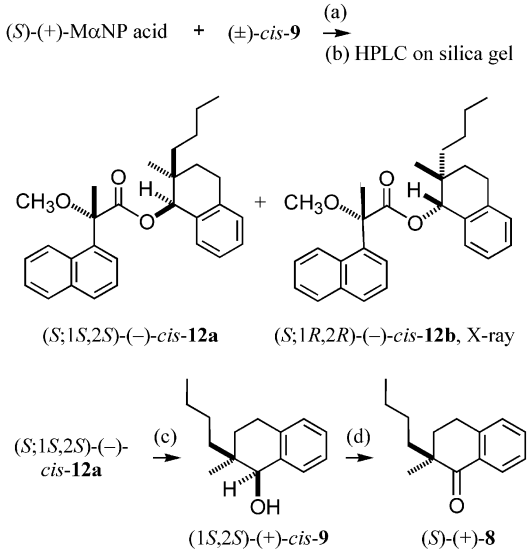


Scheme 5. Preparation of CSDP esters of *trans*-alcohol (±)-**9**, HPLC separation, and recovery of enantiopure alcohol (1*R*,2*S*)-(–)-*trans*-**9**: (a) DCC, DMAP, CH_2Cl_2. (b) HPLC on silica gel, hexane/EtOAc, 6:1, yield (1*S*,2*R*)-(–)-*trans*-**11a**, 50%, and (1*R*,2*S*)-(+)-*trans*-**11b**, 50%. (c) KOH, MeOH (96%).

Application of the MαNP Acid Method

Alcohol (±)-*cis*-**9** was esterified with (*S*)-(+)-MαNP acid giving diastereomeric esters that separated well by HPLC on silica gel (hexane/EtOAc, 15:1; separation factor α = 1.81; resolution factor R_s = 5.97), affording the first-eluted

MαNP ester (*S*:1*S*,2*S*)-(–)-*cis*-**12a** (yield 49%) and the second-eluted MαNP ester (*S*:1*R*,2*R*)-(–)-*cis*-**12b** (48%) (Scheme 6). It should be emphasized that MαNP esters **12a/12b** are very well separated as shown in Figure 3 (b) (separation factor α = 1.81). Such a large separation enables larger amount of sample to be separated by HPLC, which is a significant advantage of the MαNP ester method over the CSDP ester method.



Scheme 6. Preparation of MαNP esters of *cis*-alcohol (±)-**9**, HPLC separation, and recovery of enantiopure alcohol (1*S*,2*S*)-(+)-*cis*-**9**: (a) DCC, DMAP, CSA, CH_2Cl_2, reflux. (b) HPLC on silica gel, hexane/EtOAc, 15:1, yield (*S*:1*S*,2*S*)-(–)-*cis*-**12a**, 49%, and (*S*:1*R*,2*R*)-(–)-*cis*-**12b**, 48%. (c) NaOMe, MeOH, reflux (84%). (d) PCC, Celite, CH_2Cl_2 (92%).

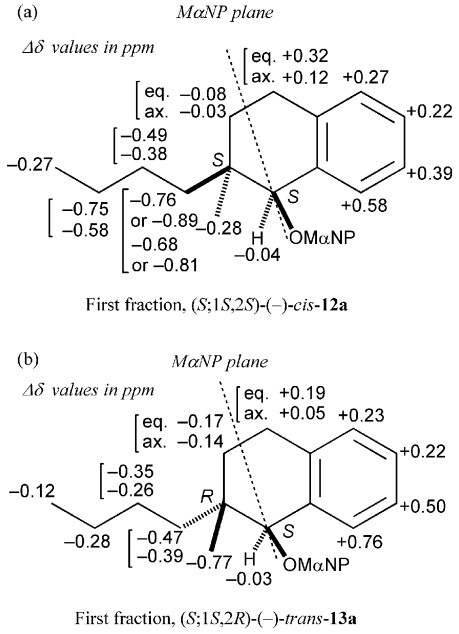


Figure 5. ^{1}H NMR anisotropy values $\Delta\delta$ [= δ(2nd fr.) – δ(1st fr.)] in ppm ($CDCl_3$) and the determination of absolute configuration: (a) first-eluted MαNP ester (*S*:1*S*,2*S*)-(–)-*cis*-**12a**; (b) first-eluted MαNP ester (*S*:1*S*,2*R*)-(–)-*trans*-**13a**.

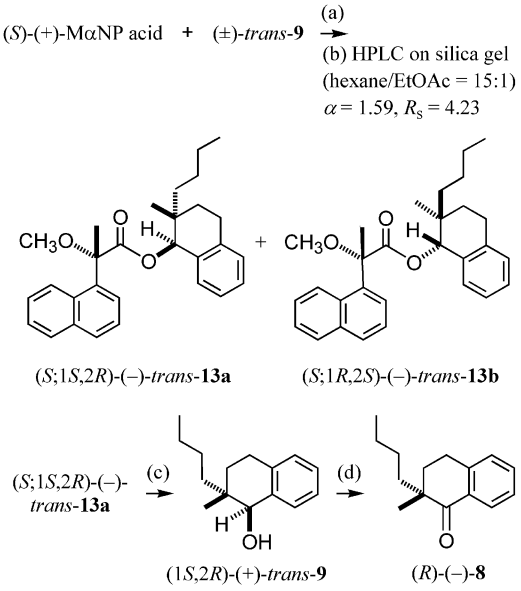
To determine the absolute configurations of MαNP esters **12a** and **12b** by using the ^{1}H NMR anisotropy method, the ^{1}H NMR spectroscopic data of both esters were carefully analyzed and assigned as listed in the Experimental Section. The anisotropy factor $\Delta\delta$ is defined as $\Delta\delta = \delta(R,X) - \delta(S,X)$, where *R* and *S* are the absolute configurations of MαNP acids used, and *X* is the absolute configuration of the alcohol to be determined. When the racemic alcohol is enantioresolved with (*S*)-(+)-MαNP acid, the anisotropy factor $\Delta\delta$ is defined as $\Delta\delta = \delta(R,X) - \delta(S,X) = \delta(S,–X) - \delta(S,X) = \delta$(2nd fr.) – δ(1st fr.), where *X* is the absolute configuration of the alcohol part in the first-eluted MαNP ester. The $\Delta\delta$ values obtained are shown in Figure 5 (a), in which the protons on the right side have positive $\Delta\delta$ values, and the protons on the left side have negative values. Based on the $\Delta\delta$ results and on the relative *cis* configuration, the absolute configuration of the first-eluted ester (–)-*cis*-**12a** was determined to be (*S*:1*S*,2*S*), and that of the second-eluted ester (–)-*cis*-**12b** was (*S*:1*R*,2*R*).

The (*S*:1*R*,2*R*) absolute configuration of the second-eluted ester (–)-*cis*-**12b** was also established by X-ray crystallographic analysis [Figure 4 (b)]; single crystals were obtained by recrystallization from hexane/EtOAc, and subjected to X-ray analysis [monoclinic, *C*2 (#5); R/R_w = 0.0425/0.0423)]. Since the ester (–)-*cis*-**12b** has no heavy atom, only the relative configuration was determined by X-ray crystallography; however, because the *S* absolute configuration of the MαNP acid part was known, the (1*R*,2*R*) absolute configuration of the alcohol part could be unambiguously determined.

Recovery of the enantiopure alcohol from the MαNP ester generally requires treatment with a stronger base (e.g., NaOMe) than required to cleave the CSDP ester. Thus, a mixture of MαNP ester (*S*:1*S*,2*S*)-(–)-**12a** and NaOMe in MeOH was heated to reflux to yield the enantiopure alcohol (1*S*,2*S*)-(+)-*cis*-**9** in good yield. It should be noted that enantiopure (*S*)-(+)-MαNP acid could be recovered from the solvolysis/hydrolysis and subsequently reused.

The ^{1}H and ^{13}C NMR spectroscopic data for the enantiopure alcohol (1*R*,2*R*)-(–)-*cis*-**9** obtained from the CSDP ester (+)-*cis*-**10b** (Scheme 4) were in complete agreement with those of alcohol (1*S*,2*S*)-(+)-*cis*-**9** recovered from the MαNP ester (–)-*cis*-**12a** (Scheme 6); however, they were opposite in the sign of specific rotation. The absolute configurational assignments by the CSDP and MαNP methods are thus consistent with each other.

Alcohol (±)-*trans*-**9** was esterified with (*S*)-(+)-MαNP acid, giving diastereomeric esters, which were similarly well separated by HPLC on silica gel (hexane/EtOAc, 15:1; separation factor α = 1.59; resolution factor R_s = 4.23) affording the first-eluted MαNP ester (*S*:1*S*,2*R*)-(–)-*trans*-**13a** (yield 47%) and the second-eluted MαNP ester (*S*:1*R*,2*S*)-(–)-*trans*-**13b** (48%) (Scheme 7). It should be noted that MαNP esters **13a/13b** were also effectively separated with a large separation factor (α = 1.59).



Scheme 7. Preparation of MαNP esters of *trans*-alcohol (±)-**9**, HPLC separation, and recovery of enantiopure alcohol (1*S*,2*R*)-(+)-*trans*-**9**: (a) DCC, DMAP, CSA, CH_2Cl_2, reflux. (b) HPLC on silica gel, hexane/EtOAc, 15:1, yield (*S*:1*S*,2*R*)-(–)-*trans*-**13a**, 47%, and (*S*:1*R*,2*S*)-(–)-*trans*-**13b**, 48%. (c) NaOMe, MeOH, reflux (81%). (d) PCC, Celite, CH_2Cl_2 (96%).

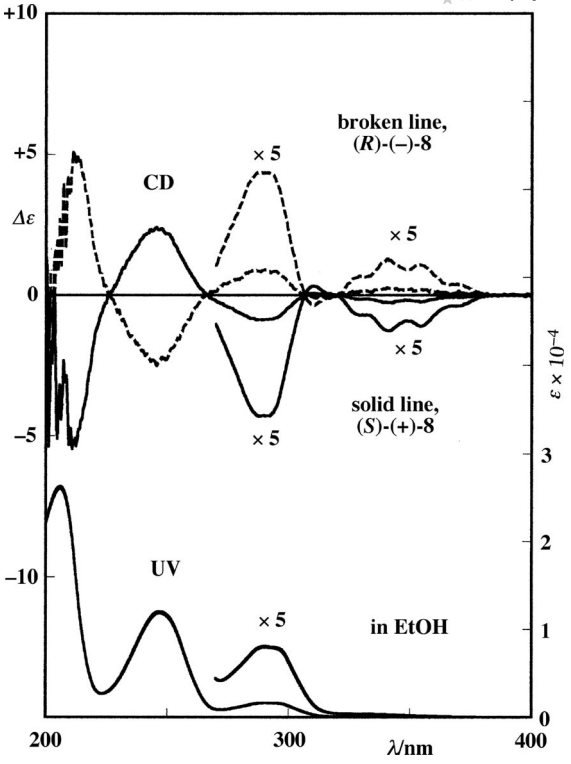


Figure 6. CD and UV spectra of aromatic ketones (*S*)-(+)-**8** and (*R*)-(–)-**8** in EtOH.

The absolute configurations of MαNP esters **13a** and **13b** were similarly determined by the ^{1}H NMR anisotropy method. As shown in Figure 5 (b), the $\Delta\delta$ values of the protons on the right side are positive, whereas those of the protons on the left side are negative. Therefore, the results led to the assignment of (*S*:1*S*,2*R*) for the absolute configuration of the first-eluted ester (–)-*trans*-**13a** and (*S*:1*R*,2*S*) configuration for the second-eluted ester (–)-*trans*-**13b**. From the first-eluted MαNP ester (–)-*trans*-**13a**, enantiopure alcohol (1*S*,2*R*)-(+)-*trans*-**9** was recovered in good yield.

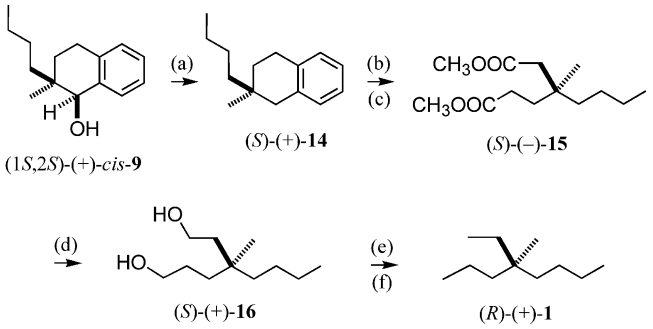
The absolute configuration of alcohol (–)-*trans*-**9** obtained from CSDP ester (+)-*trans*-**11b** (Scheme 5) was determined to be (1*R*,2*S*) by comparison with the ^{1}H and ^{13}C NMR spectra, and the specific rotation data of alcohol (1*S*,2*R*)-(+)-*trans*-**9** recovered from the MαNP ester (*S*:1*S*,2*R*)-(–)-*trans*-**13a** (Scheme 7). The absolute configurations of the compounds in Scheme 5 were thus assigned as shown by analyzing the ^{1}H NMR anisotropy and chemical correlation.

To confirm the absolute configuration of *trans*-alcohol **9** further, enantiopure alcohol (1*S*,2*S*)-(+)-*cis*-**9** was oxidized with pyridinium chlorochromate (PCC) to yield 2-butyl-2-methyl-1-tetralone (*S*)-(+)-**8** (Scheme 6). *trans*-Alcohol (1*S*,2*R*)-(+)-*trans*-**9** was similarly converted into ketone (*R*)-(–)-**8** (Scheme 7). The CD spectra obtained for both ketones were mirror images of each other, as shown in Figure 6. The absolute configuration of *trans*-alcohol **9** was thus established by chemical correlation and by X-ray crystallographic analysis.

Synthesis of Enantiopure (*R*)-(+)-[VCD(–)984]-4-Ethyl-4-methyloctane

We first synthesized racemic hydrocarbon (±)-**1** and adopted the synthetic procedure and reaction conditions shown in Scheme 8. Accordingly, enantiopure 4-ethyl-4-methyloctane (*R*)-(+)-**1** was synthesized as follows. Enantiopure alcohol (1*S*,2*S*)-(+)-*cis*-**9** was reduced with $NaBH_4$/$AlCl_3$ yielding 2-butyl-2-methyltetralin [(*S*)-(+)-**14**], the optical rotation of which was very small {$[\alpha]_D^{29}$ = +1.5 (*c* = 1.06, $CHCl_3$)}. To cleave the benzene ring, tetralin (*S*)-(+)-**14** was subjected to oxidation with HIO_4/$RuCl_3$, affording 3-butyl-3-methyladipic acid, which was isolated as dimethyl 3-butyl-3-methyladipate {(*S*)-(–)-**15**; $[\alpha]_D^{24}$ = –2.4 (*c* = 1.05, $CHCl_3$)}.

Diester (*S*)-(–)-**15** was reduced to diol (*S*)-(+)-**16** {$[\alpha]_D^{25}$ = +0.54 (*c* = 1.53, $CHCl_3$), $[\alpha]_D^{26}$ = –0.33 (*c* = 2.31, EtOH)}. It is interesting that the specific rotation of diol **16** changes its sign depending on the solvent, although the absolute values are very small. Diol (*S*)-(+)-**16** was subjected to bromination with CBr_4 and PPh_3 followed by reduction of the dibromide with $NaBH_4$ in HMPA. This furnished the target hydrocarbon, 4-ethyl-4-methyloctane {(*R*)-(+)-**1**; $[\alpha]_D^{25}$ = +0.19 (neat, ρ = 0.7565) and $[\alpha]_{365}^{23}$ = +0.70 (neat, ρ = 0.7565), where the density ρ was taken from the literature[2]}. The observed $[\alpha]_D$ and $[\alpha]_{365}$ values agreed well with the data reported by the groups of Wynberg[2] and Lardicci.[3] We have thus succeeded in the synthesis of



Scheme 8. Synthesis of enantiopure (*R*)-(+)-4-ethyl-4-methyloctane [(*R*)-(+)-**1**]: (a) $NaBH_4$, $AlCl_3$, THF, reflux (89%). (b) $RuCl_3$, HIO_4/CCl_4, CH_3CN, H_2O. (c) MeI, K_2CO_3, DMF (52%). (d) $LiAlH_4$, THF (95%). (e) CBr_4, PPh_3, CH_2Cl_2. (f) $NaBH_4$, HMPA (77%).

enantiopure 4-ethyl-4-methyloctane [(*R*)-(+)-**1**] and have, for the first time, unambiguously assigned its absolute configuration.

Direct Determination of the Structure of 4-Ethyl-4-methyloctane

As described above, our synthesis of enantiopure 4-ethyl-4-methyloctane [(*R*)-(+)-**1**] is straightforward, and its absolute configurational assignment is very clear. However, we have found a strange fact that the ^{13}C NMR spectroscopic data of (±)-**1** and (+)-**1** synthesized here disagreed with those reported by L. Lardicci and co-workers.[3] Unfortunately, H. Wynberg and a co-workers did not report the ^{13}C NMR spectroscopic data of (–)-**1**.[2]

The disagreement in the ^{13}C NMR spectroscopic data prompted us to determine the structure of **1** again by various NMR spectroscopic methods, including ^1H, ^{13}C, ^1H–^1H COSY, HMBC, and HSQC, whereby the structure was confirmed to be as shown. In addition, we conducted an HSQC–TOCSY analysis, which proved to be a much simpler and more powerful technique for the unambiguous and full assignment of the carbon and proton signals, as shown in Figure 7. For example, the ^1H triplet signal at δ = 0.89 ppm, corresponding to one of the terminal methyl groups, showed four cross peaks in the HSQC–TOCSY spectrum, which were measured using mixing times of 12, 25, and 80 ms. The results indicate that this terminal methyl group is part of the butyl group; the C-8 and 8-H_3 signals could be thus assigned. From the time dependence of the cross-peak intensity, the connectivity of C-8, C-7, C-6, and C-5 could be clearly determined, together with their chemical shift data. From the cross peaks in the HSQC, the methylene protons, 7-H_2, 6-H_2, and 5-H_2, could also be assigned.

On the other hand, the triplet signal at δ = 0.87 ppm showed three cross peaks in the HSQC–TOCSY spectrum, indicating that this methyl group is part of the propyl group; the C-1 and 1-H_3 signals could thus be assigned. From the time dependence of the cross-peak intensity, the

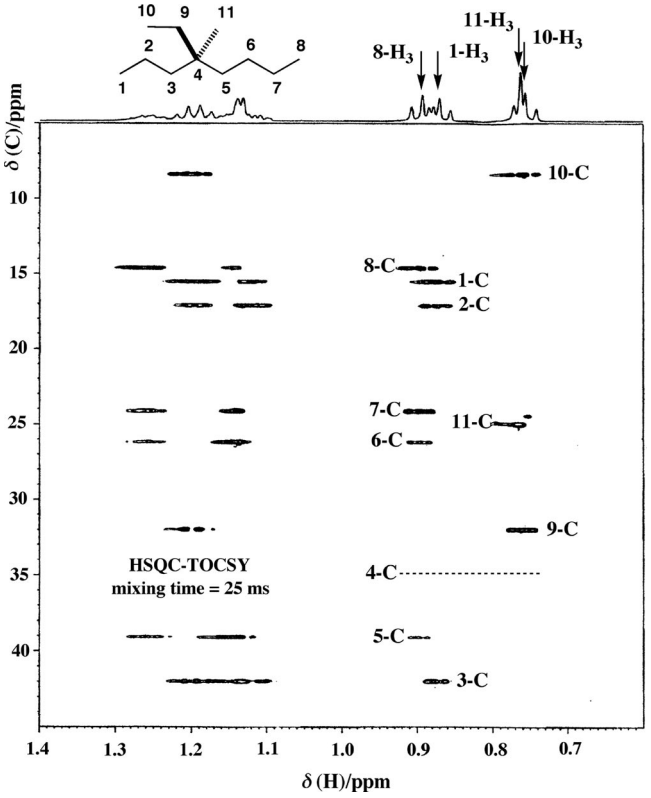


Figure 7. HSQC–TOCSY spectrum of hydrocarbon (±)-**1**: 500 MHz, $CDCl_3$, mixing time = 25 ms. There is no cross peak at δ_C = 34.8 ppm (where the quaternary carbonatom, C-4, would be expected to resonate).

connectivity of C-1, C-2, and C-3 was similarly determined, together with their chemical-shift data. From the HSQC data, the methylene protons, 2-H_2 and 3-H_2, could also be assigned.

The ^{13}C and ^1H NMR signals of the ethyl group were assigned in a similar way. The triplet signal at δ = 0.755 ppm showed two cross peaks in the HSQC–TOCSY spectrum, indicating the presence of the ethyl group; the C-10, C-9, 10-H_3, and 9-H_2 signals were thus determined. The singlet signal at δ = 0.762 ppm, showing one cross peak in the HSQC–TOCSY spectrum could clearly be assigned as the methyl group at the 4-position. The ^{13}C NMR signal at δ = 34.8 ppm showed no cross peak in the HSQC–TOCSY spectrum, and was hence assigned to the quaternary carbon atom, C-4. In consequence, all the ^1H and ^{13}C NMR signals were fully assigned as shown in Figure 7 and detailed in the Experimental Section, establishing the structure of 4-ethyl-4-methyloctane (**1**).[11] It should be emphasized that HSQC–TOCSY analysis is clearly a very powerful technique for solving the structure of compounds with complex NMR spectra.

Conclusions

We have succeeded in the synthesis of enantiopure (*R*)-(+)-4-ethyl-4-methyloctane (**1**), which is the simplest chiral saturated hydrocarbon with a quaternary chiral center, and

conducted the first unambiguous determination of its absolute configuration by X-ray crystallographic analysis, ^{1}H NMR anisotropy, and chemical correlation. The methodologies described here would be generally applicable to a range of chiral compounds containing a quaternary chiral center.

As will be discussed in Part 2 of this two-part paper,[12] VCD (i.e., the CD spectrum in the IR region) of hydrocarbon (*R*)-(+)-**1** showed a negative Cotton effect at 984 cm^{-1}. Therefore, the absolute configuration of hydrocarbon **1** can be fully designated as (*R*)-(+)-[VCD(–)984], which indicates that the enantiomer showing a negative VCD band at 984 cm^{-1} has an *R* absolute configuration.

Experimental Section

General Methods: IR spectra were obtained either neat, as a film on KBr, or as KBr disks, with a Jasco FT/IR-410 spectrophotometer. ^{1}H NMR spectra were recorded with a Jeol JNM-LA400 (400 MHz), a Bruker DMX 500 (500 MHz), and/or a Jeol JNM-LA600 (600 MHz) spectrometer. ^{13}C NMR spectra were obtained with a Jeol JNM-LA400 (100 MHz), a Bruker DMX 500 (125 MHz), and/or a Jeol JNM-LA600 (150 MHz) spectrometer. All NMR spectroscopic data of $CDCl_3$ and CD_2Cl_2 solutions are reported in ppm (δ) downfield from TMS. HR mass spectra were measured with a Jeol JMS-700TZ instrument with inlet GC (r.t., 3.53 min) operated in the EI ion mode. Optical rotations $[\alpha]_D$ were measured with a Jasco DIP-1000 spectropolarimeter. Silica gel 60 F_{254} precoated plates on glass from Merck Ltd. were used for thin layer chromatography (TLC). HPLC separation and purification were performed using a prepacked glass column (22 × 300 mm, or 25 × 400 mm) of silica gel (particle size 5–10 μm) from Kusano Co. Ltd., equipped with a UV/RI detector (Shimamura YRU-880). The purities of the title compounds were shown to be ≥99% by ^{1}H NMR, TLC, HPLC, and/or elemental analysis.

X-ray Crystallography: The diffraction measurements were carried out with a Mac Science MXC18 automated four-circle diffractometer: radiation: Cu-K_α (1.54178 Å); monochromator: graphite crystal. The structure was solved by direct methods and successive Fourier syntheses. Some hydrogen atoms were placed in calculated positions. Full-matrix least-squares refinement of positional and thermal parameters, including anomalous scattering factors of chlorine, sulfur, oxygen, nitrogen, and carbon atoms, led to the final convergence with *R* value. The absolute configuration was determined by using the CSDP acid moiety as the internal reference for the absolute configuration. The result was also supported by the anomalous dispersion effect of chlorine and sulfur atoms.

Preparation of (±)-2-Methyl-1-tetralone (7): The reported procedure[10] was modified; to a solution of diisopropylamine (1.34 mL, 10.3 mmol) in THF (20 mL) cooled to 0 °C, was added dropwise, *n*-butyllithium (1.56 M in hexane, 5.7 mL, 8.9 mmol). After cooling to –78 °C, hexamethylphosphoramide (HMPA, 5 mL) was added, and the mixture was stirred for 2 h. A solution of 1-tetralone (1.04 g, 7.08 mmol) in THF (5 mL) was added dropwise, and the mixture was stirred at –78 °C for 2 h. After addition of iodomethane (0.64 mL, 10 mmol), the mixture was stirred at –40 °C overnight. The reaction was quenched with aqueous NH_4Cl, and the mixture was extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$, water, and brine, dried with anhydrous $MgSO_4$, and the solvents were evaporated to dryness. The crude product was purified by a short column chromatography on silica gel (hexane/EtOAc, 20:1) and HPLC on silica gel (hexane/EtOAc, 50:1) yielding (±)-**7** (0.993 g, 88%); colorless oil. IR (neat): $\tilde{\nu}_{max}$ = 3066, 2963, 2932, 2861, 1685, 1602, 1455, 1376, 1359, 1323, 1268, 1228, 968, 907, 803, 776, 740 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.8 Hz, 3 H, 2-CH_3), 1.89 (dddd, *J* = 13.3, 12.0, 11.1, 4.8 Hz, 1 H, 3-H_{ax}), 2.20 (dddd, *J* = 13.3, 4.5, 4.5, 4.4 Hz, 1 H, 3-H_{eq}), 2.60 (ddq, *J* = 12.0, 4.4, 6.8 Hz, 1 H, 2-H), 2.97 (br. ddd, *J* = 16.8, 4.8, 4.5 Hz, 1 H, 4-H_{eq}), 3.05 (br. ddd, *J* = 16.8, 11.1, 4.5 Hz, 1 H, 4-H_{ax}), 7.23 (br. d, *J* = 7.5 Hz, 1 H), 7.30 (br. dd, *J* = 7.8, 7.5 Hz, 1 H), 7.46 (ddd, *J* = 7.5, 7.5, 1.3 Hz, 1 H), 8.04 (dd, *J* = 7.8, 1.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.34, 28.82, 31.35, 42.62, 126.53, 127.38, 128.69, 132.37, 133.06, 144.18, 200.80 ppm. $C_{11}H_{12}O$ (160.21): calcd. C 82.46, H 7.55; found C 81.97, H 7.60.

Preparation of (±)-2-Butyl-2-methyl-1-tetralone (8): A mixture of 2-methyl-1-tetralone (±)-**7** (2.81 g, 17.5 mmol) and *t*BuOK (3.21 g, 26.3 mmol) in THF (50 mL) was heated to reflux for 2 h. After cooling to r.t., 1-iodobutane (3.99 mL, 26.3 mmol) was added, and the mixture was stirred for 1 h. Aqueous saturated NH_4Cl was added and the mixture was extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$, water, and brine, dried with anhydrous $MgSO_4$, and then concentrated to dryness. The crude product was purified by short column chromatography on silica gel (hexane/EtOAc, 20:1) and by HPLC on silica gel (hexane/EtOAc, 50:1) yielding (±)-**8** (2.79 g, 74%); colorless oil. IR (neat): $\tilde{\nu}_{max}$ = 2961, 2932, 2860, 1683, 1601, 1455, 1376, 1302, 1221, 1155, 1100, 965, 900, 741 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (br. t, *J* = 7.0 Hz, 3 H, terminal CH_3), 1.18 (s, 3 H, 2-CH_3), 1.21–1.34 (m, 4 H), 1.50 (m, 1 H), 1.64 (m, 1 H), 1.92 (ddd, *J* = 13.7, 8.4, 5.2 Hz, 1 H, 3-H_{ax}), 2.08 (ddd, *J* = 13.7, 6.8, 5.1 Hz, 1 H, 3-H_{eq}), 2.93 (br. ddd, *J* = 17.3, 6.8, 5.2 Hz, 1 H, 4-H_{eq}), 3.00 (br. ddd, *J* = 17.3, 8.4, 5.1 Hz, 1 H, 4-H_{ax}), 7.21 (br. d, *J* = 7.5 Hz, 1 H), 7.30 (br. dd, *J* = 7.9, 7.4 Hz, 1 H), 7.45 (ddd, *J* = 7.5, 7.4, 1.3 Hz, 1 H), 8.04 (dd, *J* = 7.9, 1.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.02, 22.16, 23.33, 25.38, 26.14, 33.65, 36.09, 44.63, 126.54, 127.95, 128.60, 131.72, 132.88, 143.29, 202.78 ppm. $C_{15}H_{20}O$ (216.32): calcd. C 83.28, H 9.32; found C 83.07, H 9.13.

Preparation of (±)-2-Butyl-2-methyl-1-tetralols (*cis*-9 and *trans*-9): To a solution of ketone (±)-**8** (1.38 g, 6.40 mmol) in THF (20 mL) cooled to 0 °C, was added portion-wise, $LiAlH_4$ (0.239 g, 6.28 mmol), and the mixture was stirred at r.t. overnight. The excess hydride was quenched by the dropwise addition of aqueous diethyl ether, and the organic layer was separated from the precipitate, which was washed with diethyl ether. The combined organic layers were dried with anhydrous $MgSO_4$, and the solvents were evaporated to dryness. The epimeric alcohols formed were purified by short column chromatography on silica gel (hexane/EtOAc, 10:1) and then separated by HPLC on silica gel (hexane/EtOAc, 15:1) yielding (±)-*cis*-**9** (0.962 g, 69%) and (±)-*trans*-**9** (0.431 g, 31%).

(±)-*cis*-Alcohol 9: Colorless oil. IR (neat): $\tilde{\nu}_{max}$ = 3396, 2955, 2931, 2860, 1456, 1378, 1020, 946, 771, 739 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (s, 3 H, 2-CH_3), 0.93 (br. t, *J* = 7.1 Hz, 3 H, terminal CH_3), 1.25–1.52 (m, 8 H), 1.85 (ddd, *J* = 13.7, 8.1, 7.3 Hz, 1 H, 3-H_{ax}), 2.75 (br. ddd, *J* = 18.0, 8.1, 6.5 Hz, 1 H, 4-H_{ax}), 2.80 (br. ddd, *J* = 18.0, 7.3, 5.8 Hz, 1 H, 4-H_{eq}), 4.29 (br. d, *J* = 5.8 Hz, 1 H, 1-H), 7.11 (m, 1 H), 7.17–7.22 (m, 2 H), 7.39 (m, 1 H) ppm. ^{1}H NMR NOE (400 MHz, $CDCl_3$): irradiation of H with signal at δ = 4.29 ppm => +4.8% NOE of Me signal at δ = 0.89 ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.23, 21.28, 23.67, 25.53, 25.72, 29.34, 35.76, 36.02, 75.93, 126.12, 127.43, 128.80, 129.37, 136.29,

138.26 ppm. $C_{15}H_{22}O$ (218.33): calcd. C 82.52, H 10.16; found C 82.33, H 10.04.

(±)-*trans*-Alcohol 9: Colorless solid. IR (film): $\tilde{\nu}_{max}$ = 3383, 2956, 2929, 2859, 1491, 1455, 1378, 1040, 1009, 772, 737 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (br. t, J = 7.1 Hz, 3 H, terminal CH_3), 0.97 (s, 3 H, 2-CH_3), 1.22–1.35 (m, 6 H), 1.56 (br. ddd, J = 13.5, 6.8, 6.5 Hz, 1 H, 3-H), 1.64 (m, 1 H), 1.78 (ddd, J = 13.5, 7.5, 6.3 Hz, 1 H, 3-H), 2.71 (br. ddd, J = 17.8, 7.5, 6.8 Hz, 1 H, 4-H), 2.79 (br. ddd, J = 17.8, 6.5, 6.3 Hz, 1 H, 4-H), 4.30 (br. d, J = 5.6 Hz, 1 H, 1-H), 7.10 (m, 1 H), 7.16–7.22 (m, 1 H), 7.44 (m, 1 H) ppm. ^1H NMR NOE (400 MHz, $CDCl_3$): irradiation of H with signal at δ = 4.30 ppm => +7.5% NOE of 2 H signal at δ = 1.22–1.35 ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.15, 19.81, 23.56, 25.74, 25.80, 28.96, 36.33, 37.46, 75.64, 126.12, 127.26, 128.68, 128.99, 136.06, 138.58 ppm. $C_{15}H_{22}O$ (218.33): calcd. C 82.52, H 10.16; found C 82.43, H 10.00.

Preparation and Separation of CSDP Esters (1*S*,2*S*)-(–)-*cis*-10a and (1*R*,2*R*)-(+)-*cis*-10b: To a mixture of racemic alcohol (±)-*cis*-**9** (0.052 g, 0.24 mmol), (–)-CSDP acid (0.206 g, 0.477 mmol), 4-(dimethylamino)pyridine (DMAP; 0.018 g, 0.15 mmol), and 1,3-dicyclohexylcarbodiimide (DCC; 0.120 g, 0.582 mmol) cooled to 0 °C, was added CH_2Cl_2 (1 mL), and the mixture was stirred at r.t. overnight. The excess DCC was hydrolyzed with a small amount of water and, after addition of anhydrous $MgSO_4$, the mixture was filtered through Celite, and the filtrate was concentrated to dryness. The diastereomeric CSDP esters were purified by short column chromatography on silica gel (hexane/EtOAc, ca. 1:1) and then separated by HPLC on silica gel (hexane/EtOAc, 6:1; α = 1.17, R_s = 1.51) yielding (1*S*,2*S*)-(–)-*cis*-**10a** (0.078 g, 50%) and (1*R*,2*R*)-(+)-*cis*-**10b** (0.074 g, 47%).

CSDP Ester (1*S*,2*S*)-(–)-*cis*-10a: Colorless plates; m.p. 142–144 °C. $[\alpha]_D^{25}$ = –122 (c = 1.07, $CHCl_3$). IR (film): $\tilde{\nu}_{max}$ = 2959, 1722, 1687, 1587, 1553, 1457, 1376, 1337, 1298, 1264, 1245, 1168, 1142, 1116, 1094, 1064, 972, 910, 758, 733, 649, 540 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (br. t, J = 6.8 Hz, 3 H, terminal CH_3), 0.93 (s, 3 H), 0.98 (s, 3 H), 1.24–1.47 (m, 11 H), 1.65 (br. ddd, J = 13.7, 7.1, 6.0 Hz, 1 H, 3-H), 1.92–2.01 (m, 3 H), 1.98 (br. ddd, J = 13.7, 7.7, 6.2 Hz, 1 H, 3-H), 2.14 (m, 1 H), 2.52 (m, 1 H), 2.82 (br. ddd, J = 17.7, 7.7, 7.1 Hz, 1 H, 4-H), 2.91 (br. ddd, J = 17.7, 6.2, 6.0 Hz, 1 H, 4-H), 3.37 (d, J = 13.9 Hz, 1 H), 3.42 (d, J = 13.9 Hz, 1 H), 3.96 (m, 1 H), 5.90 (s, 1 H, 1-H), 7.10–7.15 (m, 2 H), 7.19–7.27 (m, 2 H), 7.53 (s, 1 H), 7.96 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.16, 20.06, 20.83, 21.35, 23.48, 25.40, 26.50, 29.55, 33.02, 35.58, 35.88, 37.50, 44.68, 47.75, 48.43, 53.06, 65.54, 78.84, 126.08, 127.96, 128.72, 128.91, 129.85, 131.09, 131.28, 133.82, 134.70, 135.04, 136.58, 136.74, 163.06, 165.24 ppm. UV (EtOH): λ_{max} (ε) = 295.4 (700), 244.2 (13000), 215.0 (44200 $L\,mol^{-1}\,cm^{-1}$) nm. CD (EtOH): λ_{ext} ($\Delta\varepsilon$) = 250.2 (–16.6), 219.4 (+41.9 $L\,mol^{-1}\,cm^{-1}$) nm. $C_{33}H_{39}Cl_2NO_5S$ (632.64): calcd. C 62.65, H 6.21, Cl 11.21, N 2.21, S 5.07; found C 61.48, H 6.30, Cl 9.92, N 2.11, S 4.44.

CSDP Ester (1*R*,2*R*)-(+)-*cis*-10b: Colorless prisms; m.p. 190–191 °C (EtOH/CH_2Cl_2). $[\alpha]_D^{25}$ = +21.0 (c = 1.02, $CHCl_3$). IR (film): $\tilde{\nu}_{max}$ = 2958, 1722, 1686, 1553, 1458, 1337, 1299, 1244, 1168, 1142, 1116, 1093, 1064, 972, 909, 733, 652, 538 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, J = 7.0 Hz, 3 H, terminal CH_3), 0.93 (s, 3 H), 0.96 (s, 3 H), 1.23–1.45 (m, 11 H), 1.67 (br. ddd, J = 13.7, 6.4, 6.0 Hz, 1 H, 3-H_{eq}), 1.89–1.95 (m, 3 H), 1.99 (br. ddd, J = 13.7, 8.1, 6.1 Hz, 1 H, 3-H_{ax}), 2.15 (m, 1 H), 2.53 (m, 1 H), 2.83 (br. ddd, J = 17.6, 8.1, 6.4 Hz, 1 H, 4-H_{ax}), 2.90 (br. ddd, J = 17.6, 6.1, 6.0 Hz, 1 H, 4-H_{eq}), 3.27 (d, J = 13.7 Hz, 1 H), 3.40 (d, J = 13.7 Hz, 1 H), 3.91 (m, 1 H), 5.96 (s, 1 H, 1-H), 7.12 (br. dd, J = 7.8, 7.5 Hz, 1 H), 7.13 (br. d, J = 7.8 Hz, 1 H), 7.21 (br. ddd, J = 7.5, 7.4, 1.3 Hz, 1 H), 7.31 (br. d, J = 7.4 Hz, 1 H), 7.49 (s, 1 H), 8.07 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.13, 20.04, 20.97, 21.19, 23.49, 25.44, 25.64, 26.47, 29.66, 32.93, 36.01, 36.21, 37.65, 44.79, 47.72, 48.45, 52.91, 65.54, 78.60, 126.01, 128.00, 128.39, 128.64, 130.29, 131.04, 131.61, 133.81, 134.59, 135.07, 136.74, 136.77, 162.91, 165.17 ppm. UV (EtOH): λ_{max} (ε) = 295.2 (800), 244.2 (12700), 215.2 (43100 $L\,mol^{-1}\,cm^{-1}$) nm. CD (EtOH): λ_{ext} ($\Delta\varepsilon$) = 241.8 (–2.8), 220.2 (–16.2 $L\,mol^{-1}\,cm^{-1}$) nm. $C_{33}H_{39}Cl_2NO_5S$ (632.64): calcd. C 62.65, H 6.21, Cl 11.21, N 2.21, S 5.07; found C 62.51, H 6.15, Cl 11.79, N 2.21, S 5.02.

X-ray Data of CSDP Ester (1*R*,2*R*)-(+)-*cis*-10b: Crystallized from EtOH/CH_2Cl_2; crystal dimension: 0.38 × 0.37 × 0.32 mm; crystal system: orthorhombic; space group: $P2_12_12_1$ (#19); a = 11.306(2) Å, b = 25.590(5) Å, c = 11.250(3) Å; V = 3255(1) $Å^3$; Z = 4; $D_{calcd.}$ = 1.291 g/cm^3; D_{obsd} = 1.285 g/cm^3; no. of independent reflections: $F_o > 3.0\sigma(F_o)$, 3135; no. of variables: 443; R/R_w = 0.0598/0.0740; R/R_w for the mirror image = 0.0719/0.0899. CCDC-753557 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Preparation and Separation of CSDP Esters (1*S*,2*R*)-(–)-*trans*-11a and (1*R*,2*S*)-(+)-*trans*-11b: The CSDP esters were prepared and separated as described above for the *cis* esters: HPLC on silica gel (hexane/EtOAc, 6:1; α = 1.12, R_s = 1.10) yielded (1*S*,2*R*)-(–)-*trans*-**11a** (50%) and (1*R*,2*S*)-(+)-*trans*-**11b** (50%).

CSDP Ester (1*S*,2*R*)-(–)-*trans*-11a: Colorless solid. $[\alpha]_D^{25}$ = –163 (c = 1.06, $CHCl_3$). IR (film): $\tilde{\nu}_{max}$ = 2959, 1720, 1686, 1588, 1553, 1457, 1376, 1337, 1298, 1142, 1116, 1094, 1064, 974, 909, 768, 733, 649, 540 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (br. t, J = 6.8 Hz, 3 H, terminal CH_3), 0.98 (s, 3 H), 0.99 (s, 3 H), 1.24–1.46 (m, 11 H), 1.62 (m, 1 H), 1.88–1.94 (m, 3 H), 1.98 (br. ddd, J = 13.9, 10.4, 6.4 Hz, 1 H, 3-H_{ax}), 2.14 (m, 1 H), 2.52 (m, 1 H), 2.80 (br. ddd, J = 17.7, 10.4, 6.7 Hz, 1 H, 4-H_{ax}), 2.88 (br. ddd, J = 17.7, 6.4, 4.7 Hz, 1 H, 4-H_{eq}), 3.37 (d, J = 13.8 Hz, 1 H), 3.43 (d, J = 13.8 Hz, 1 H), 3.92 (m, 1 H), 5.90 (s, 1 H, 1-H), 7.13 (br. dd, J = 7.6, 7.0 Hz, 1 H), 7.15 (br. d, J = 7.0 Hz, 1 H), 7.23 (br. ddd, J = 7.7, 7.6, 1.4 Hz, 1 H), 7.28 (br. d, J = 7.7 Hz, 1 H), 7.52 (s, 1 H), 7.92 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.10, 20.04, 20.82, 21.58, 23.38, 25.59, 25.79, 26.47, 29.96, 33.02, 35.86, 35.89, 37.47, 44.68, 47.74, 48.39, 53.05, 65.51, 78.09, 126.11, 128.12, 128.77, 128.97, 130.67, 131.05, 131.27, 133.65, 134.65, 134.98, 136.52, 136.74, 163.10, 165.25 ppm. UV (EtOH): λ_{max} (ε) = 297.0 (600), 244.0 (13700), 215.0 (46000 $L\,mol^{-1}\,cm^{-1}$) nm. CD (EtOH): λ_{ext} ($\Delta\varepsilon$) = 249.2 (–18.3), 218.8 (+38.1 $L\,mol^{-1}\,cm^{-1}$) nm. $C_{33}H_{39}Cl_2NO_5S$ (632.64): calcd. C 62.65, H 6.21, Cl 11.21, N 2.21, S 5.07; found C 62.03, H 6.18, Cl 11.17, N 2.14, S 5.12.

CSDP Ester (1*R*,2*S*)-(+)-*trans*-11b: Colorless solid. $[\alpha]_D^{25}$ = +33.2 (c = 1.11, $CHCl_3$). IR (film): $\tilde{\nu}_{max}$ = 2959, 1722, 1687, 1588, 1553, 1457, 1377, 1337, 1299, 1244, 1168, 1142, 1116, 1094, 1064, 974, 909, 768, 734, 651, 539 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, J = 7.1 Hz, 3 H, terminal CH_3), 0.96 (s, 3 H), 0.99 (s, 3 H), 1.17–1.38 (m, 11 H), 1.67 (br. ddd, J = 13.7, 6.1, 5.7 Hz, 1 H, 3-H_{eq}), 1.88–1.92 (m, 3 H), 1.96 (br. ddd, J = 13.7, 9.2, 6.1 Hz, 1 H, 3-H_{ax}), 2.14 (br. dd, J = 13.7, 8.1 Hz, 1 H), 2.54 (m, 1 H), 2.81 (br. ddd, J = 17.7, 9.2, 6.1 Hz, 1 H, 4-H_{ax}), 2.88 (br. ddd, J = 17.7, 6.1, 5.7 Hz, 1 H, 4-H_{eq}), 3.26 (d, J = 13.6 Hz, 1 H), 3.40 (d, J = 13.6 Hz, 1 H), 3.87 (m, 1 H), 5.97 (s, 1 H, 1-H), 7.13 (br. dd, J = 7.3, 7.2 Hz, 1 H), 7.14 (br. d, J = 7.2 Hz, 1 H), 7.22 (br. ddd, J = 7.4, 7.3, 1.6 Hz, 1 H), 7.28 (br. d, J = 7.4 Hz, 1 H), 7.47 (s, 1 H), 8.08 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.08, 20.00, 20.93,

21.32, 23.35, 25.58, 25.73, 26.41, 29.09, 32.88, 36.17, 36.28, 37.60, 44.76, 47.67, 48.39, 52.86, 65.48, 78.04, 125.98, 128.01, 128.34, 128.62, 130.60, 130.97, 131.63, 133.72, 134.56, 135.01, 136.71, 136.73, 162.92, 165.15 ppm. UV (EtOH): λ_{max} (ε) = 297.0 (600), 244.2 (13700), 215.0 (46000 L mol^{-1} cm^{-1}) nm. CD (EtOH): λ_{ext} ($\Delta\varepsilon$) = 262.0 (–1.8), 240.0 (–2.8), 220.4 (–15.7 L mol^{-1} cm^{-1}) nm. $C_{33}H_{39}Cl_2NO_5S$ (632.64): calcd. C 62.65, H 6.21, Cl 11.21, N 2.21, S 5.07; found C 62.13, H 6.19, Cl 11.46, N 2.16, S 5.26.

Recovery of Enantiopure 2-Butyl-2-methyl-1-tetralol (1*R*,2*R*)-(–)-*cis*-9 from CSDP Ester (1*R*,2*R*)-(+)-*cis*-10b: A mixture of (1*R*,2*R*)-(+)-*cis*-**10b** (0.730 g, 1.15 mmol) in saturated KOH/MeOH solution (16 mL) was stirred at r.t. overnight. After addition of water, the mixture was extracted with diethyl ether. The organic layer was dried with anhydrous $MgSO_4$, and the solvents were evaporated to dryness. The crude product was purified by short column chromatography on silica gel (hexane/EtOAc, 10:1) yielding alcohol (1*R*,2*R*)-(–)-*cis*-**9** (0.221 g, 88%) as a colorless oil. $[\alpha]_D^{29}$ = –11.6 (*c* = 1.31, $CHCl_3$). The IR, ^{1}H NMR, and ^{13}C NMR were identical with those of racemate (±)-*cis*-**9**. UV (EtOH): λ_{max} (ε) = 272.8 (300), 265.4 (400), 212.4 (8900 L mol^{-1} cm^{-1}) nm. CD (EtOH): λ_{ext} ($\Delta\varepsilon$) = 272.4 (+0.10), 264.8 (+0.08 L mol^{-1} cm^{-1}) nm. $C_{15}H_{22}O$ (218.33): calcd. C 82.52, H 10.16; found C 82.23, H 10.21.

Recovery of Enantiopure 2-Butyl-2-methyl-1-tetralol (1*R*,2*S*)-(–)-*trans*-9 from CSDP Ester (1*R*,2*S*)-(+)-*trans*-11b: CSDP ester (1*R*,2*S*)-(+)-*trans*-**11b** was treated as described for the *cis* ester, yielding (1*R*,2*S*)-(–)-*trans*-**9** (96%) as a colorless oil. $[\alpha]_D^{29}$ = –9.7 (*c* = 1.02, $CHCl_3$). The IR, ^{1}H NMR, and ^{13}C NMR were identical with those of racemate (±)-*trans*-**9**. UV (EtOH): λ_{max} (ε) = 272.8 (300), 265.4 (400), 213.4 (8800 L mol^{-1} cm^{-1}) nm. CD (EtOH) was almost silent. $C_{15}H_{22}O$ (218.33): calcd. C 82.52, H 10.16; found C 82.20, H 10.26.

Preparation and Separation of MαNP Esters (*S*:1*S*,2*S*)-(–)-*cis*-12a and (*S*:1*R*,2*R*)-(–)-*cis*-12b: To a mixture of racemic alcohol (±)-*cis*-**9** (0.875 g, 4.01 mmol), (*S*)-(+)-MαNP acid (1.10 g, 4.80 mmol), DMAP (1.01 g, 8.28 mmol), 10-camphorsulfonic acid (CSA; 0.812 g, 3.75 mmol), and DCC (2.49 g, 12.1 mmol) cooled to 0 °C, was added CH_2Cl_2 (10 mL), and the mixture was heated gently to reflux overnight. The excess DCC was hydrolyzed by addition of a small amount of water. After addition of anhydrous $MgSO_4$, the mixture was filtered through Celite, and the filtrate was concentrated to dryness. The diastereomeric MαNP esters were purified by short column chromatography on silica gel (hexane/EtOAc, ca. 1:1) and then separated by HPLC on silica gel (hexane/EtOAc, 15:1; α = 1.81, R_s = 5.97) yielding (*S*:1*S*,2S)-(–)-*cis*-**12a** (0.853 g, 49%) and (*S*:1*R*,2R)-(–)-*cis*-**12b** (0.830 g, 48%).

MαNP Ester (*S*:1*S*,2*S*)-(–)-*cis*-12a: Colorless solid. $[\alpha]_D^{25}$ = –87.7 (*c* = 1.09, $CHCl_3$). IR (film): $\tilde{\nu}_{max}$ = 2934, 1861, 1727, 1600, 1510, 1494, 1457, 1380, 1344, 1248, 1180, 1134, 1052, 970, 915, 805, 778, 732 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.78 (s, 3 H, 13-H_3), 0.86 (br. t, *J* = 7.0 Hz, 3 H, 12-H_3), 1.04 (m, 1 H, 9-H), 1.17 (m, 5 H, 9-H, 10-H_2, 11-H_2), 1.31 (dddd, *J* = 13.5, 6.6, 5.7, 0.8 Hz, 1 H, 3-H_{eq}), 1.41 (ddd, *J* = 13.5, 8.7, 6.7 Hz, 1 H, 3-H_{ax}), 2.00 (s, 3 H, CH_3), 2.35 (br. ddd, *J* = 17.5, 6.7, 5.7 Hz, 1 H, 4-H_{eq}), 2.51 (br. ddd, *J* = 17.5, 8.7, 6.6 Hz, 1 H, 4-H_{ax}), 3.07 (s, 3 H, OCH_3), 5.65 (br. s, 1 H, 1-H), 6.73 (br. ddd, *J* = 7.5, 7.3, 1.2 Hz, 1 H, 7-H), 6.76 (dd, *J* = 7.5, 1.7 Hz, 1 H, 8-H), 6.79 (br. d, *J* = 7.4 Hz, 1 H, 5-H), 6.98 (ddd, *J* = 7.4, 7.3, 1.7 Hz, 1 H, 6-H), 7.23 (ddd, *J* = 8.7, 6.9, 1.5 Hz, 1 H), 7.34 (dd, *J* = 8.2, 7.3 Hz, 1 H), 7.36 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1 H), 7.50 (dd, *J* = 7.3, 1.1 Hz, 1 H), 7.73 (br. d, *J* = 8.2 Hz, 1 H), 7.75 (br. dd, *J* = 8.2, 1.5 Hz, 1 H), 8.24 (br. dd, *J* = 8.7, 1.2 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.14, 20.97, 21.84, 23.48, 25.10, 25.25, 29.70, 35.57, 36.38, 50.92, 77.61, 81.80, 124.42, 125.22, 125.24, 125.38, 125.41, 126.23, 127.47, 128.16, 128.29, 129.12, 129.74, 131.17, 133.32, 133.85, 135.02, 136.22, 173.32 ppm. UV (EtOH): λ_{max} (ε) = 294.0 (4600), 282.2 (6700), 272.6 (5800), 224.8 (59500), 222.8 (56300 L mol^{-1} cm^{-1}) nm. CD (EtOH): λ_{ext} ($\Delta\varepsilon$) = 282.0 (+0.8), 224.8 (–43.3 L mol^{-1} cm^{-1}) nm. $C_{29}H_{34}O_3$ (430.58): calcd. C 80.89, H 7.96; found C 80.81, H 8.13.

MαNP Ester (*S*;1*R*,2*R*)-(–)-*cis*-12b: Colorless prisms (hexane/EtOAc). $[\alpha]_D^{25}$ = –7.7 (*c* = 1.11, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 2933, 1744, 1457, 1367, 1245, 1134, 971, 920, 805, 781 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.28 (ddd, *J* = 13.1, 12.7, 4.7 Hz, 1 H, 9-H), 0.36 (ddd, *J* = 13.1, 12.7, 4.0 Hz, 1 H, 9-H), 0.42 (m, 1 H, 11-H), 0.50 (s, 3 H, 13-H_3), 0.59 (m, 4 H, 11-H, 12-H_3), 0.68 (m, 1 H, 10-H), 0.79 (ddddd, *J* = 16.8, 12.7, 4.7, 4.7, 4.7 Hz, 1 H, 10-H), 1.23 (dddd, *J* = 13.4, 6.0, 5.0, 0.9 Hz, 1 H, 3-H_{eq}), 1.38 (ddd, *J* = 13.4, 9.2, 6.9 Hz, 1 H, 3-H_{ax}), 1.80 (s, 3 H, CH_3), 2.63–2.67 (br. ddd, *J* = 17.5, 9.2, 6.0 Hz, 2 H, 4-H_2), 3.04 (s, 3 H, OCH_3), 5.61 (br. s, 1 H, 1-H), 7.06 (br. d, *J* = 7.6 Hz, 1 H, 5-H), 7.12 (br. ddd, *J* = 7.6, 7.5, 1.1 Hz, 1 H, 7-H), 7.20 (br. ddd, *J* = 7.6, 7.5, 1.3 Hz, 1 H, 6-H), 7.34 (br. dd, *J* = 7.6, 1.3 Hz, 1 H, 8-H), 7.41 (dd, *J* = 8.1, 7.1 Hz, 1 H), 7.44 (m, 1 H), 7.48 (dd, *J* = 7.1, 1.2 Hz, 1 H), 7.56 (m, 1 H), 7.81 (br. d, *J* = 8.1 Hz, 1 H), 7.83 (m, 1 H), 8.56 (m, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.08, 20.19, 21.35, 22.88, 24.93, 25.45, 29.27, 35.15, 36.38, 50.61, 77.13, 81.45, 124.52, 125.72, 125.75, 125.84, 125.98, 126.55, 127.87, 128.45, 128.62, 129.40, 130.14, 131.61, 133.97, 134.24, 134.77, 136.63, 173.20 ppm. UV (EtOH): λ_{max} (ε) = 293.6 (5100), 282.2 (7300), 272.8 (6400), 224.8 (70300), 222.0 (65400 L mol^{-1} cm^{-1}) nm. CD (EtOH): λ_{ext} ($\Delta\varepsilon$) = 293.4 (–2.8), 282.4 (–4.2), 271.0 (–2.8), 226.2 (+5.3), 209.6 (–24.1 L mol^{-1} cm^{-1}) nm. $C_{29}H_{34}O_3$ (430.58): calcd. C 80.89, H 7.96; found C 80.81, H 8.13.

Preparation and Separation of MαNP Esters (*S*:1*S*,2*R*)-(–)-*trans*-13a and (*S*:1*R*,2*S*)-(–)-*trans*-13b: The MαNP esters were prepared and separated as described above for the *cis* esters: HPLC on silica gel (hexane/EtOAc, 15:1; α = 1.59, R_s = 4.23) yielded (*S*:1*S*,2*R*)-(–)-*trans*-**13a** (47%) and (*S*:1*R*,2*S*)-(–)-*trans*-**13b** (48%).

MαNP Ester (*S*:1*S*,2*R*)-(–)-*trans*-13a: Colorless solid. $[\alpha]_D^{27}$ = –86.9 (*c* = 1.13, $CHCl_3$). IR (film): $\tilde{\nu}_{max}$ = 3051, 2933, 2860, 1743, 1600, 1510, 1494, 1456, 1378, 1344, 1241, 1180, 1134, 1051, 993, 966, 936, 805, 779 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.77 (s, 3 H, 13-H_3), 0.83 (br. t, *J* = 7.1 Hz, 3 H, 12-H_3), 1.14 (m, 2 H, 9-H_2), 1.19 (m, 2 H, 11-H_2), 1.23 (m, 2 H, 10-H_2), 1.43 (dd, *J* = 7.3, 6.2 Hz, 2 H, 3-H_2), 2.03 (s, 3 H, CH_3), 2.43 (dt, *J* = 17.4, 6.2 Hz, 1 H, 4-H_{eq}), 2.52 (dt, *J* = 17.4, 7.3 Hz, 1 H, 4-H_{ax}), 3.11 (s, 3 H, OCH_3), 5.69 (br. s, 1 H, 1-H), 6.50 (br. d, *J* = 7.6 Hz, 1 H, 8-H), 6.63 (br. ddd, *J* = 7.6, 7.5, 1.0 Hz, 1 H, 7-H), 6.82 (br. d, *J* = 7.5 Hz, 1 H, 5-H), 6.96 (br. ddd, *J* = 7.5, 7.5, 1.3 Hz, 1 H, 6-H), 7.34 (ddd, *J* = 8.6, 6.9, 1.5 Hz, 1 H), 7.34 (dd, *J* = 8.1, 7.3 Hz, 1 H), 7.42 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1 H), 7.52 (dd, *J* = 7.3, 1.0 Hz, 1 H), 7.74 (br. d, *J* = 8.1 Hz, 1 H), 7.78 (br. dd, *J* = 8.1, 1.5 Hz, 1 H), 8.38 (br. dd, *J* = 8.6, 1.2 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.07, 20.90, 21.95, 23.39, 25.22, 25.55, 29.18, 35.86, 36.74, 50.97, 77.34, 81.89, 124.51, 125.30, 125.43, 125.51, 125.56, 126.34, 127.27, 128.13, 128.42, 129.20, 129.33, 131.31, 133.61, 133.94, 134.92, 136.05, 173.48 ppm. UV (EtOH): λ_{max} (ε) = 294.0 (4400), 282.2 (6500), 272.8 (5700), 224.8 (58200), 222.0 (54100 L mol^{-1} cm^{-1}) nm. CD (EtOH): λ_{ext} ($\Delta\varepsilon$) = 284.4 (+0.6), 224.2 (–47.8 L mol^{-1} cm^{-1}) nm. $C_{29}H_{34}O_3$ (430.58): calcd. C 80.89, H 7.96; found C 80.32, H 7.99.

MαNP Ester (*S*:1*R*,2*S*)-(–)-*trans*-13b: Colorless solid. $[\alpha]_D^{27}$ = –8.6 (*c* = 1.06, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3053, 2932, 2857, 1744, 1600, 1509, 1494, 1456, 1367, 1238, 1181, 1137, 1053, 992, 938, 805,

780 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 0.00 (s, 3 H, 13-H_3), 0.67 (ddd, J = 13.5, 12.1, 4.3 Hz, 1 H, 9-H), 0.71 (t, J = 6.8 Hz, 3 H, 12-H_3), 0.75 (ddd, J = 13.5, 12.0, 4.4 Hz, 1 H, 9-H), 0.88 (m, 1 H, 10-H), 0.91 (ddq, J = 6.8, 6.8, 6.8 Hz, 2 H, 11-H_2), 0.97 (m, 1 H, 10-H), 1.26 (ddd, J = 13.6, 6.9, 6.1 Hz, 1 H, 3-H_{eq}), 1.29 (ddd, J = 13.6, 8.1, 6.1 Hz, 1 H, 3-H_{ax}), 1.90 (s, 3 H, CH_3), 2.57 (br. ddd, J = 17.4, 8.1, 6.9 Hz, 1 H, 4-H_{ax}), 2.62 (br. ddd, J = 17.4, 6.1, 6.1 Hz, 1 H, 4-H_{eq}), 3.08 (s, 3 H, OCH_3), 5.66 (br. s, 1 H, 1-H), 7.05 (br. d, J = 7.4 Hz, 1 H, 5-H), 7.13 (br. ddd, J = 7.5, 7.5, 1.3 Hz, 1 H, 7-H), 7.18 (ddd, J = 7.5, 7.4, 1.4 Hz, 1 H, 6-H), 7.26 (br. d, J = 7.5 Hz, 1 H, 8-H), 7.41 (dd, J = 8.1, 7.3 Hz, 1 H), 7.45 (m, 1 H), 7.46 (m, 1 H), 7.50 (dd, J = 7.3, 1.1 Hz, 1 H), 7.81 (br. d, J = 8.1 Hz, 1 H), 7.83 (m, 1 H), 8.58 (m, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.02, 19.79, 21.42, 23.09, 25.39, 25.43, 28.92, 35.39, 36.10, 50.66, 76.98, 81.51, 124.53, 125.72, 125.83, 125.89, 126.01, 126.55, 127.64, 128.42, 128.60, 129.38, 129.62, 131.71, 133.95, 134.44, 134.82, 136.59, 173.53 ppm. UV (EtOH): λ_{max} (ε) = 293.2 (4600), 282.2 (6700), 272.6 (5800), 224.6 (62700), 222.4 (59200 L mol^{-1} cm^{-1}) nm. CD (EtOH): λ_{ext} ($\Delta\varepsilon$) = 283.4 (–2.0), 281.2 (–3.2), 270.6 (–2.5), 236.6 (+2.0), 218.6 (–20.2 L mol^{-1} cm^{-1}) nm. $C_{29}H_{34}O_3$ (430.58): calcd. C 80.89, H 7.96; found C 80.13, H 7.94.

Recovery of Enantiopure 2-Butyl-2-methyl-1-tetralol (1*S*,2*S*)-(+)-*cis*-9 from MαNP Ester (*S*:1*S*,2*S*)-(–)-*cis*-12a: A mixture of (*S*:1*S*,2*S*)-(–)-*cis*-**12a** (0.325 g, 0.755 mmol) and NaOMe/MeOH solution (28%, 5 mL) was gently heated to reflux overnight. After the reaction was quenched with water, the mixture was extracted with diethyl ether three times, and the organic layer was dried with anhydrous $MgSO_4$, and the solvents were evaporated to dryness. The crude product was purified by short column chromatography on silica gel (hexane/EtOAc, 5:1) and HPLC on silica gel (hexane/EtOAc, 20:1) yielding alcohol (1*S*,2*S*)-(+)-*cis*-**9** (0.139 g, 84%) as a colorless oil. $[a]_D^{28}$ = +10.8 (c = 1.26, $CHCl_3$). The IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of racemate (±)-*cis*-**9**. UV (EtOH): λ_{max} (ε) = 272.8 (300), 264.8 (400), 213.2 (8800 L mol^{-1} cm^{-1}) nm. CD (EtOH): λ_{ext} ($\Delta\varepsilon$) = 272.8 (–0.10), 264.8 (–0.07 L mol^{-1} cm^{-1}) nm. $C_{15}H_{22}O$ (218.33): calcd. C 82.52, H 10.16; found C 82.14, H 10.21. The addition of 2 M HCl to the aqueous layer gave a white precipitate, which was collected by filtration and dried yielding (*S*)-(+)-MαNP acid (0.134 g, 77%).

Recovery of Enantiopure 2-Butyl-2-methyl-1-tetralol (1*S*,2*R*)-(+)-*trans*-9 from MαNP Ester (*S*:1*S*,2*R*)-(–)-*trans*-13a: Ester (*S*:1*S*,2*R*)-(–)-*trans*-**13a** was treated as described for the *cis* ester, yielding alcohol (1*S*,2*R*)-(+)-*trans*-**9** (81%) as a colorless oil. $[a]_D^{26}$ = +9.4 (c = 1.06, $CHCl_3$). The IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of racemate (±)-*trans*-**9**. UV (EtOH): λ_{max} (ε) = 272.8 (300), 264.8 (400), 213.2 (8800 L mol^{-1} cm^{-1}) nm. CD (EtOH) was almost silent. $C_{15}H_{22}O$ (218.33): calcd. C 82.52, H 10.16; found C 82.20, H 10.26. (*S*)-(+)-MαNP acid (96%) was recovered from the aqueous layer.

Preparation of Enantiopure 2-Butyl-2-methyl-1-tetralone (*S*)-(+)-(8) from Alcohol (1*S*,2*S*)-(+)-*cis*-9: A mixture of alcohol (1*S*,2*S*)-(+)-*cis*-**9** (0.056 g, 0.26 mmol) and pyridinium chlorochromate (PCC; 0.177 g, 0.819 mmol) in CH_2Cl_2 (2.5 mL) was stirred at r.t. for 8 h. After addition of diethyl ether, the mixture was filtered through Celite, and the solvents were evaporated to dryness. The crude product was purified by short column chromatography on silica gel (hexane/EtOAc, 20:1) and HPLC on silica gel (hexane/EtOAc, 50:1) to give ketone (*S*)-(+)-**8** (0.052 g, 92%) as a colorless oil. $[a]_D^{32}$ = +7.9 (c = 1.45, $CHCl_3$). The IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of racemate (±)-**8**. UV (EtOH): λ_{max} (ε) = 289.8 (1600), 247.0 (11900), 206.0 (26000 L mol^{-1} cm^{-1}) nm. CD (EtOH): λ_{ext} ($\Delta\varepsilon$) = 354.4 (–0.22), 341.4 (–0.26), 328.2 (–0.14), 309.8 (+0.06), 286.8 (–0.89), 245.6 (+2.40), 210.8 (–5.45 L mol^{-1} cm^{-1}) nm. $C_{15}H_{20}O$ (216.32): calcd. C 83.28, H 9.32; found C 83.01, H 9.30.

Preparation of Enantiopure 2-Butyl-2-methyl-1-tetralone (*R*)-(–)-(8) from Alcohol (1*S*,2*R*)-(+)-*trans*-9: Alcohol (1*S*,2*R*)-(+)-*trans*-**9** was treated as described for *cis* alcohol, yielding ketone (*R*)-(–)-**8** (96%) as a colorless oil. $[a]_D^{30}$ = –8.4 (c = 1.19, $CHCl_3$). The IR, ^1H NMR, and ^{13}C NMR spectra were identical with those of racemate (±)-**8**. UV (EtOH): λ_{max} (ε) = 290.2 (1700), 247.0 (12100), 206.0 (26300 L mol^{-1} cm^{-1}) nm. CD (EtOH): λ_{ext} ($\Delta\varepsilon$) = 354.0 (+0.22), 340.8 (+0.26), 329.2 (+0.14), 310.6 (–0.07), 287.4 (+0.87), 245.6 (–2.52), 211.2 (+5.07 L mol^{-1} cm^{-1}) nm. $C_{15}H_{20}O$ (216.32): calcd. C 83.28, H 9.32; found C 83.08, H 9.65.

Preparation of Enantiopure 2-Butyl-2-methyltetralin (*S*)-(+)-14: A mixture of alcohol (1*S*,2*S*)-(+)-*cis*-**9** (0.536 g, 2.46 mmol), $NaBH_4$ (0.513 g, 13.6 mmol), anhydrous $AlCl_3$ (1.56 g, 11.6 mmol), and THF (26 mL) was gently heated to reflux for 2 h. After the reaction was quenched with water at 0 °C, the mixture was diluted with EtOAc, and the organic layer was dried with anhydrous $MgSO_4$, and the solvents were evaporated to dryness. The crude product was purified by short column chromatography on silica gel (hexane) and HPLC on silica gel (hexane) to yield (*S*)-(+)-2-butyl-2-methyltetralin (**14**; 0.443 g, 89%) as a colorless oil. $[a]_D^{29}$ = +1.5 (c = 1.06, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2956, 2927, 2870, 1495, 1456, 1377, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (br. t, J = 7.0 Hz, 3 H, terminal CH_3), 0.92 (s, 3 H, 2-CH_3), 1.20–1.33 (m, 6 H), 1.54 (ddt, J = 13.1, 1.1, 6.6 Hz, 1 H, 3-H), 1.60 (dt, J = 13.1, 6.6 Hz, 1 H, 3-H), 2.48 (d, J = 16.2 Hz, 1 H, 1-H), 2.57 (d, J = 16.2 Hz, 1 H, 1-H), 2.77 (br. t, J = 6.6 Hz, 2 H, 4-H_2), 7.01–7.10 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.21, 23.61, 24.63, 25.86, 26.18, 31.84, 33.89, 40.83, 42.33, 125.29, 125.42, 128.69, 129.56, 136.08, 136.44 ppm. UV (EtOH): λ_{max} (ε) = 273.2 (600), 266.2 (600), 212.2 (8400 L mol^{-1} cm^{-1}) nm. CD (EtOH): λ_{ext} ($\Delta\varepsilon$) = 273.0 (–0.05), 265.2 (–0.06 L mol^{-1} cm^{-1}) nm. $C_{15}H_{22}$ (202.34): calcd. C 89.04, H 10.96; found C 88.49, H 11.10.

Preparation of Enantiopure Dimethyl 3-Butyl-3-methyladipate (*S*)-(–)-15: To a mixture of 2-butyl-2-methyltetralin (*S*)-(+)-**14** (0.496 g, 2.45 mmol), CCl_4 (4.9 mL), CH_3CN (4.9 mL), and water (7.4 mL), was added $HIO_4/2H_2O$ (8.23 g, 36.1 mmol), and the mixture was stirred until it became a clear solution. $RuCl_3$/hydrate (0.017 g, 0.081 mmol) was added to give a brown solution, which was stirred at r.t. overnight. The reaction mixture was extracted with EtOAc three times, and the organic layer was dried with anhydrous $MgSO_4$, and the solvents were evaporated to dryness to give the crude dicarboxylic acid (0.131 g). A mixture of the crude dicarboxylic acid, K_2CO_3 (11.3 g, 81.4 mmol), *N*,*N*-dimethylformamide (DMF; 15 mL), and iodomethane (5.5 mL, 88 mmol) was stirred at r.t. overnight. After addition of diethyl ether, the mixture was filtered through Celite, and the filtrate was concentrated to dryness. The yellow oil obtained was dissolved in diethyl ether, and the solution was dried with anhydrous $MgSO_4$, filtered, and the solvents were evaporated to dryness. The crude ester product was purified by HPLC on silica gel (hexane/EtOAc, 15:1) to yield dimethyl 3-butyl-3-methyladipate (*S*)-(–)-**15** (0.309 g, 52%) as a colorless oil. $[a]_D^{24}$ = –2.4 (c = 1.05, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2956, 2873, 1739, 1437, 1382, 1237, 1198, 1168, 1017 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (br. t, J = 6.7 Hz, 3 H, terminal CH_3), 0.97 (s, 3 H, 3-CH_3), 1.18–1.30 (m, 6 H), 1.68 (m, 2 H), 2.21 (br. s, 2 H), 2.30 (m, 2 H), 3.65 (s, 3 H, OCH_3), 3.67 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.04, 23.33, 24.66, 25.66, 28.96, 34.10, 35.33, 39.00, 43.45, 51.20, 51.60, 172.38, 174.38 ppm.

Preparation of Enantiopure 3-Butyl-3-methyl-1,6-hexanediol (*S*)-(+)-16: To a solution of dimethyl 3-butyl-3-methyladipate (*S*)-(–)-**15** (0.239 g, 0.978 mmol) in THF (10 mL) cooled to 0 °C, was added $LiAlH_4$ (0.053 g, 1.4 mmol), and the mixture was stirred at r.t. overnight. After the reaction was quenched with diethyl ether/water, the organic layer was dried with anhydrous $MgSO_4$, and the solvents were evaporated to dryness giving the crude product, which was purified by HPLC on silica gel (hexane/EtOAc/*i*PrOH, 10:20:2) to yield 3-butyl-3-methyl-1,6-hexanediol (*S*)-(+)-**16** (0.174 g, 95%) as a colorless solid. $[\alpha]_D^{25}$ = +0.54 (*c* = 1.53, $CHCl_3$). $[\alpha]_D^{26}$ = –0.33 (*c* = 2.31, EtOH). IR (film): $\tilde{\nu}_{max}$ = 3320, 2931, 2863, 1457, 1373, 1054, 1014, 672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 3 H, 3-CH_3), 0.90 (br. t, *J* = 7.0 Hz, 3 H, terminal CH_3), 1.19–1.56 (m, 12 H), 3.62 (t, *J* = 6.5 Hz, 2 H), 3.68 (br. t, *J* = 7.7 Hz, 2 H) ppm. ^1H NMR (400 MHz, [D_6]DMSO): δ = 0.79 (s, 3 H, 3-CH_3), 0.87 (t, *J* = 7.2 Hz, 3 H, terminal CH_3), 1.10–1.36 (m, 12 H), 3.31–3.38 (m, 2 H), 3.39 (br. dt, *J* = 5.1, 7.8 Hz, 2 H), 4.22 (t, *J* = 5.1 Hz, 1 H, OH), 4.36 (t, *J* = 5.1 Hz, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.11, 23.52, 25.21, 25.68, 26.87, 34.21, 35.45, 39.47, 41.90, 59.46, 63.63 ppm.

Preparation of Enantiopure 4-Ethyl-4-methyloctane (*R*)-(+)-1: To a solution of 3-butyl-3-methyl-1,6-hexanediol (*S*)-(+)-**16** (0.139 g, 0.740 mmol) and triphenylphosphane (PPh_3; 0.815 g, 3.11 mmol) in CH_2Cl_2 (2 mL) cooled to 0 °C, was added CBr_4 (0.723 g, 2.18 mmol), and the mixture was stirred at 0 °C for 0.5 h and then at r.t. for 2 h. The reaction mixture was directly subjected to short column chromatography on silica gel (hexane) to yield the crude dibromoalkane (0.367 g) as a colorless oil. To a mixture of the crude dibromoalkane (0.367 g) and HMPA (2 mL), was added $NaBH_4$ (0.266 g, 7.03 mmol), and the mixture was stirred at r.t. for 2 h. The reaction mixture was directly subjected to a short column chromatography on silica gel, which was eluted with pentane (60 mL), and the eluent was concentrated under atmospheric pressure to yield 4-ethyl-4-methyloctane (*R*)-(+)-**1** (0.089 g, 77%) as a colorless liquid. $[\alpha]_D^{25}$ = +0.19 (neat, ρ = 0.7565), $[\alpha]_{365}^{23}$ = +0.70 (neat, ρ = 0.7565). ^1H NMR (400 MHz, CD_2Cl_2): δ = 0.76 (t, *J* = 7.4 Hz, 3 H), 0.77 (s, 3 H), 0.87 (t, *J* = 7.0 Hz, 3 H), 0.89 (t, *J* = 7.2 Hz, 3 H), 1.10–1.30 (m, 12 H) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 8.10, 14.35, 15.25, 17.04, 24.12, 24.70, 26.12, 31.90, 35.15, 38.99, 41.90 ppm. HRMS: *m/z* calcd. for $C_{11}H_{24}$ $[M]^+$ 156.1878; found 156.1863.

Preparation of Racemic 4-Ethyl-4-methyloctane (±)-1: Starting from racemic alcohol (±)-*cis*-**9**, racemic 4-ethyl-4-methyloctane (±)-**1** was synthesized as described above as a colorless liquid; b.p. 183–184 °C. IR (neat): $\tilde{\nu}_{max}$ = 2961, 2928, 2857, 1459 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.76 (t, *J* = 7.6 Hz, 3 H), 0.76 (s, 3 H), 0.87 (t, *J* = 7.1 Hz, 3 H), 0.89 (t, *J* = 7.2 Hz, 3 H), 1.09–1.30 (m, 12 H) ppm. ^1H NMR (400 MHz, CD_2Cl_2): δ = 0.76 (t, *J* = 7.6 Hz, 3 H), 0.77 (s, 3 H), 0.87 (t, *J* = 7.0 Hz, 3 H), 0.90 (t, *J* = 7.2 Hz, 3 H), 1.10–1.31 (m, 12 H) ppm. ^1H NMR (600 MHz, $CDCl_3$): δ = 0.76 (t, *J* = 7.5 Hz, 3 H, 10-H_3), 0.76 (s, 3 H, 11-H_3), 0.87 (t, *J* = 7.2 Hz, 3 H, 1-H_3), 0.89 (t, *J* = 7.2 Hz, 3 H, 8-H_3), 1.11 (t, *J* = 7.2 Hz, 2 H, 3-H_2), 1.14 (m, 2 H, 6-H_2), 1.14 (m, 2 H, 5-H_2), 1.20 (tq, *J* = 7.2, 7.2 Hz, 2 H, 2-H_2), 1.20 (q, *J* = 7.5 Hz, 2 H, 9-H_2), 1.26 (m, 2 H, 7-H_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.93 (C-10), 14.17 (C-8), 15.07 (C-1), 16.64 (C-2), 23.68 (C-7), 24.52 (C-11), 25.72 (C-6), 31.50 (C-9), 34.82 (C-4), 38.61 (C-5), 41.51 (C-3) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 8.10, 14.35, 15.25, 17.04, 24.11, 24.69, 26.12, 31.90, 35.15, 38.99, 41.90 ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 7.99 (C-10), 14.23 (C-8), 15.13 (C-1), 16.71 (C-2), 23.74 (C-7), 24.58 (C-11), 25.79 (C-6), 31.58 (C-9), 34.89 (C-4), 38.69 (C-5), 41.59 (C-3) ppm.

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[11] After the publication of our short communication,[6] we received private information from a third party that the Lardicci group had made an error in interpreting the ^{13}C NMR spectroscopic data. Namely, they had misassigned the signal at δ = 7.9 ppm to be the TMS peak and, therefore, their chemical shift data should be corrected by addition of 7.9 ppm. If this is the case, their data agree well with ours except for the last, lowest-field peak, which may arise from some impurity.

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