^{1}H NMR Determination of Absolute Configuration of 1- or 2-Aryl-Substituted Alcohols and Amines by Means of Their Diastereomers: Novel Separation Technique of Diastereomeric Derivatives of Pyridyl Alcohols by Extraction

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Abstract: A convenient method to determine the absolute configuration of *trans*-2-aryl cyclohexanols, 1-aryl alcohols and amines was achieved. This method takes advantage of the ^{1}H NMR spectroscopic observations of the remarkable high-field shift of C18-CH_3 protons caused by the aromatic shielding effect. It is based on a discrimination of the difference of the environments in two diastereomers derived from 3β-acetoxy-5-etienic acid. Furthermore, it was observed that the corresponding diastereomeric derivatives of the pyridyl alcohols were simply separated by extraction based on the difference in their basicity.

Keywords: CH – pi interaction · configuration determination · diastereomer extraction · NMR spectroscopy

Introduction

Determination of the absolute configuration of chiral alcohols, amines and their analogues is one of the important subjects in organic chemistry,[1] since many biologically active compounds are associated with a chiral sense dependence on the activities.[2] X-ray crystallographic analysis or ^{1}H NMR spectroscopic analysis, represented by the modified Mosher method,[3] have been frequently used methods to determine the absolute configuration in this field. The serious drawback of an X-ray crystallographic analysis is the necessity to obtain high-quality single crystals of the target molecule; this is sometimes associated with difficulties. Although the modified Mosher method is an excellent method to determine the absolute configuration, with some exceptions,[4] it requires the preparation of both corresponding diastereomeric esters with α-methoxy-α-trifluoromethylphenylacetic acid. Because of these circumstances, we have described a convenient ^{1}H NMR spectroscopic method to determine the absolute configuration of some aryl-substituted alcohols and amines[5] that is based on the observations of the remarkable shielding effect which discriminates between the environments in two diastereomers[6] in the optically active molecules. We also described the distinguishing difference in the pK_a values of the diastereomeric derivatives of *trans*-2-pyridylcyclohexanols, which allows a simple separation by extraction.[7] This skillful technique is the first example of the separation of diastereomers by extraction with achiral media. We now describe the full account of these studies, in which a connection for the chiral discrimination between the CH moiety and the π moiety is described.[8]

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author, and includes ^{1}H NMR spectra of **3a** and **4a** at various temperatures, and the NOESY spectrum of **3a**.

Results and Discussion

Our first interest was to explore the possibility of discriminating the environments in two diastereomers by an intramolecular CH – π interaction in a chiral environment. The CH – π interaction,[9] which was proposed by Nishio et al. in

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1977,[10] is an attractive force between a soft acid and a soft base, and it provided an important contribution to the understanding of weak intramolecular forces and their potential value to the physical, chemical and biochemical sciences.[9e] First of all, we planned an ^{1}H NMR analysis of compounds **3** and **4**, which both bear a CH moiety, derived from the optically active 3β-acetoxy-5-etienic acid,[11] and a π moiety, derived from the (±)-*trans*-2-arylcyclohexanol derivative,[12] in the same molecule (Scheme 1).

In this system, we expected an effective intramolecular attractive force based on a CH–π interaction between the aromatic ring moiety of the racemic alcohols and the β-methyl moiety at the 18-position (C18-CH_3) of the optically active steroid ring that exists only in the (1*S*, 2*R*) isomer **3a**.[13] A molecular orbital analysis of the compounds **3a** and **4a** by MO calculation (PM3)[14] suggested this possibility, as depicted in Figure 1.

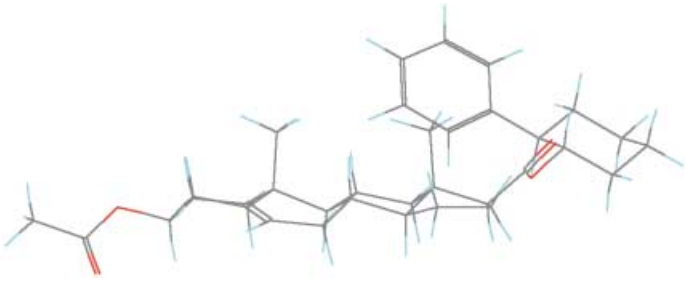
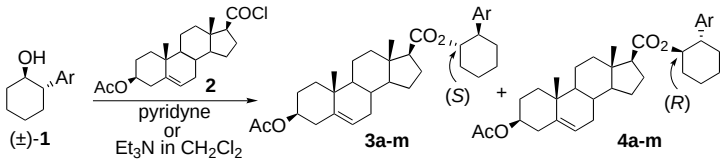


Figure 1. Calculated conformation of (1*S*, 2*R*) isomer **3a** showing CH–π interaction.



Scheme 1. Diastereomeric derivatives (**3** and **4**) derived from 3β-acetoxy-5-etienic acid and (±)-*trans*-2-arylcyclohexanols (acylation of (±)-**1** with steroid compound **2**).

With the above postulation in mind, we prepared a mixture of the two diastereomeric esters, **3a** and **4a**, from (±)-*trans*-2-phenyl-1-cyclohexanol. As shown in Figure 2, the ^{1}H NMR spectrum of the mixture indicated that the chemical shift ($\delta = 0.039$) of the β-methyl at the 18-position (C18-CH_3) of one isomer is quite different from that of the other isomer ($\delta = 0.449$). This suggests that the two methyl groups are in quite different environments.

To determine which isomer shows the remarkable high-field shift, the stereo-defined compound **3a** was prepared from the enantiomerically pure (1*S*, 2*R*)-alcohol **1a**. Consistent with the prediction from the MO calculations, the β-methyl protons at the 18-position appeared at an unusually high field in the ^{1}H NMR spectrum ($\delta = 0.039$; Figure 3). Therefore, it is reasonable to consider that that the unusual high-field shift is derived from a CH–π interaction. In addition, **3a** showed a red shift of the E_1 absorption relative to that of **4a** in the UV spectrum in acetonitrile (λ_{max}: 192 and

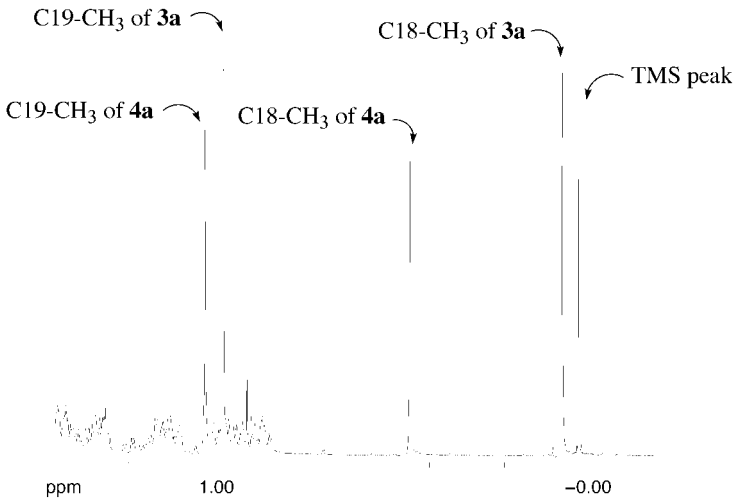


Figure 2. Partial ^{1}H NMR spectrum (600 MHz) of a mixture of diastereomeric isomers **3a** and **4a** in $CDCl_3$ at 25 °C.

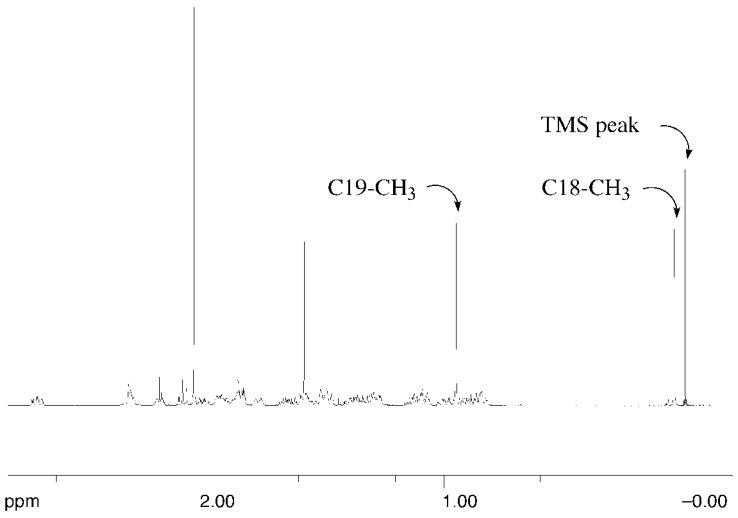


Figure 3. Partial ^{1}H NMR spectrum (600 MHz) of (1*S*,2*R*) isomer **3a** in $CDCl_3$ at 25 °C.

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187 nm, respectively),[15] which supports the consideration of the unusual high-field shift ($\delta = 0.039$) derived from an affinity, such as a CH–π interaction.[16]

Interestingly, these remarkable high-field shifts of C18-CH_3 in the (1*S*, 2*R*) isomer were also observed when other deuterium solvents, such as [D_4]methanol and [D_6]benzene, were used. The absolute values of the difference in the chemical shifts of C18-CH_3 between the *S* isomer and *R* isomer obtained from each deuterium solvent is an indication that $CDCl_3$ was the most effective medium for the phenomenon (Table 1).

Table 1. Chemical shifts of C18-CH_3 of **3a** and **4a** in various deuterated solvents at 25 °C.

Solvent	δ_H **3a**	δ_H **4a**	$\Delta\delta_H$
$CDCl_3$	0.039	0.449	0.410
CD_3OD	0.045	0.430	0.385
C_6D_6	0.305	0.601	0.296

More clear-cut evidence for the CH–π interaction was obtained by an X-ray crystallographic analysis of the (1*S*, 2*R*) isomer **3c** (Figure 4).[17] The β-methyl at the 18-position was found to be placed in close proximity to the π face of the anisyl group.[18] The closest interatomic distance between the CH moiety and the aromatic π plane was shorter (2.92 Å) than the sum of the van der Waals radii.[19] We assume that the trigger of this interaction may fix the conformation to the *ap* plane of the chiral esters,[20] and hence the interaction function is superior to the steric effect between the CH and π moieties. The NOESY spectrum in $CDCl_3$ also supported the close proximity between the CH moiety and π moiety.[21] Hence, it seems that the structure in the solid state is retained in solution.

Furthermore, the ^{1}H NMR spectra of the variable temperature conditions showed that the value of the chemical shift of C18-CH_3 moved to a higher field as the temperature was lowered ($\delta = -0.077$ at −60 °C versus $\delta = 0.043$ at 23 °C). This phenomenon appears to be the result of the transformation of the molecule to the more stable CH–π conformation as the molecular momentum decreased with decreasing temperature (Table 2).

Table 2. Chemical shifts of β-CH_3 at various temperatures.

Compound	Position	δ in $CDCl_3$			
		23 °C	0 °C	−30 °C	−60 °C
3a	C18-CH_3	0.043	0.005	−0.040	−0.077
	C19-CH_3	0.946	0.943	0.942	0.946
4a	C18-CH_3	0.450	0.443	0.438	0.438

On the other hand, almost no change was observed in the same variable temperature range in the ^{1}H NMR of **4a** derived from the (1*R*, 2*S*)-alcohol regarding the chemical shift value of C18-CH_3. The X-ray crystallographic analysis of compound **4c** showed the absence of a similar CH–π interaction in this molecule (Figure 5).

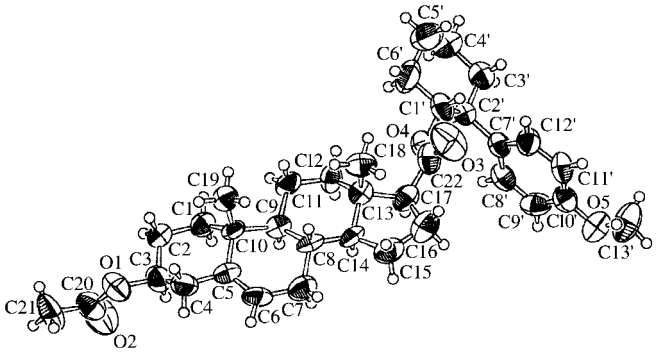


Figure 5. ORTEP drawing of (1*R*, 2*S*)-**4c**.

These findings led us to assume that a molecule for which such an interaction is observed in the ^{1}H NMR spectrum must always have the (1*S*, 2*R*) configuration, since an intramolecular CH–π interaction requires a highly ordered conformation. To verify our hypothesis, we performed, as a further example, an X-ray crystallographic analysis to determine the absolute configuration of the resolved chiral alcohol **1f** of the corresponding diastereomer **3f**, which showed a CH–π interaction in the NMR spectrum, bearing the (1*S*, 2*R*) configuration (Table 3, entry 6). From the results, the determination of the configurations by means of the CH–π interaction also seems to hold for other 2-arylcyclohexanols.[22] This method has the advantage that it can easily predict the absolute configuration with only one diastereomer, since the degree of high-field shift is abnormal.

Further examples are given in Table 3.[20] Note that the alcohols bearing the various aromatic moieties, such as naphthyl and heteroaryl functions, showed remarkable higher field shifts (Table 3, entries 5–13). These results seem to suggest that the high electron density of the aromatic moiety and/or the spreadability of the π plane lead to a significant CH–π interaction.[23].

It is worth noting that the LAH reduction of the individual diastereomer (**3** or **4**) gave the corresponding optically pure alcohol[24] in an almost quantitative yield, suggesting that the

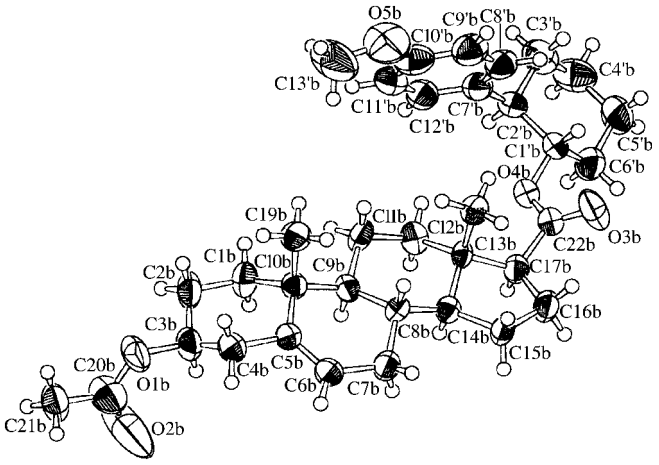


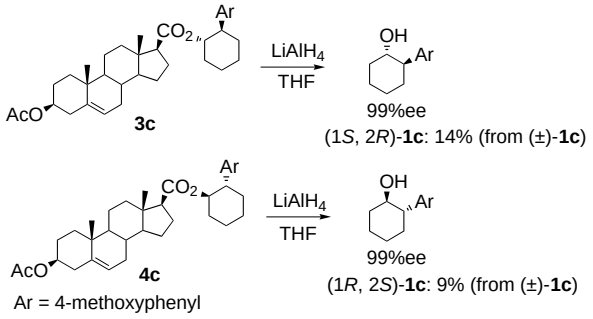
Figure 4. ORTEP drawing of (1*S*, 2*R*)-**3c**.

Table 3. ^{1}H NMR spectroscopic determination of the absolute configuration by means of the intramolecular CH – π interaction.

Entry	Ar		Yield [%][a]	δ_H of C18-CH_3 in **3** or **4**[b]	Predicted configuration of resolved **1**
1	Ph	**3a**	85	0.039	*S*[c]
		4a		0.449	*R*
2	*p*-tolyl	**3b**	74	0.068	*S*
		4b		0.481	*R*
3	4-methoxyphenyl	**3c**	77	0.006	*S*[d]
		4c		0.490	*R*
4	4-chlorophenyl	**3d**	66	0.116	*S*
		4d		0.486	*R*
5	1-naphthyl	**3e**	59	– 0.214	*S*
		4e		0.322	*R*
6	2-naphthyl	**3f**	33	– 0.246	*S*[d]
		4f		0.426	*R*
7	2-pyridyl	**3g**	92	0.115	*S*
		4g		0.463	*R*
8	2-(3′-methylpyridyl)	**3h**	73	0.128	*S*
		4h		0.443	*R*
9	2-(4′-methylpyridyl)	**3i**	87	0.098	*S*[d]
		4i		0.464	*R*
10	2-(5′-methylpyridyl)	**3j**	84	0.136	*S*
		4j		0.490	*R*
11	2-(6′-methylpyridyl)	**3k**	82	0.073	*S*
		4k		0.463	*R*
12	2-(4′-chloropyridyl)	**3l**	96	0.128	*S*
		4l		0.479	*R*
13	2-quinolyl	**3m**	91	– 0.226	*S*
		4m		0.421	*R*

[a] Isolated yields of a mixture of diastereomers by column chromatography. [b] 25 °C in $CDCl_3$. [c] The configuration was confirmed by use of an enantiomerically pure substrate with known absolute configuration. [d] The configuration was confirmed by X-ray crystallographic analysis.

enantiomerically pure **1**[9b] could be obtained by the removal of the steroid moiety after recrystallisation, which could cause a diastereomeric excess (*de*; Scheme 2). An example is shown in Figure 6.



Scheme 2. Removal of steroid moiety.

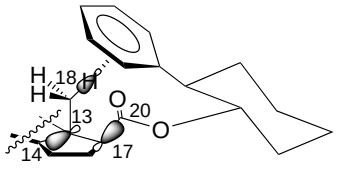


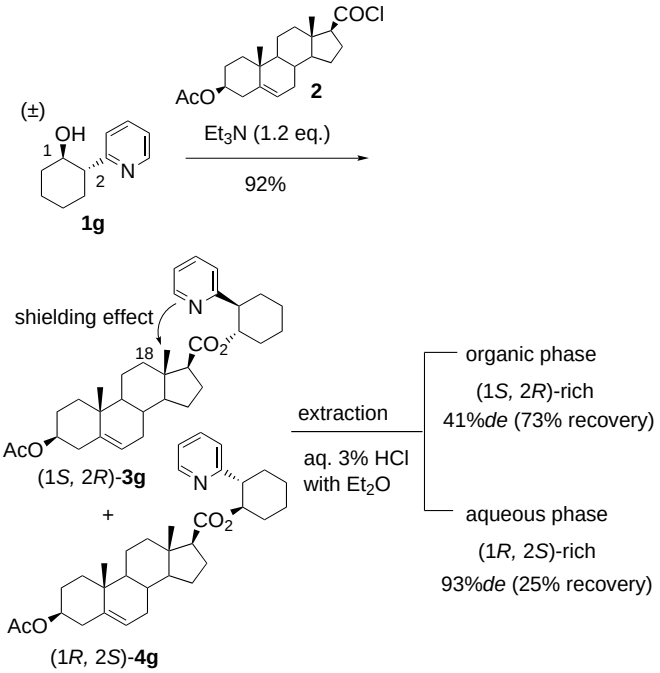
Figure 6. Speculation: contribution of stereoelectronic effect.

We assume that the stereoelectronic effect and/or the rigidity of the configuration induced by the adjacent carbonyl group also exerts such a strong CH – π interaction in the esters **3** (Figure 6). For instance, the red shift of the linked ester–carbonyl moiety of the diastereomers **3a** in the IR spectra supports the possibility of such a successive stereoelectronic effect ($\nu = 1727$ cm^{-1} in **3a** versus 1734 cm^{-1} in **4a**). Although recent reports concerning the calculations of the simple intermolecular CH – π interaction suggest that the origin of the interaction is the dispersion force rather than charge-transfer force[25] and the stabilising energy is less than 1 kcal mol^{-1}, we guess that the CH – π interaction we observed is a special case based on the contribution of the effective stereoelectronic effect.

If an interaction, such as charge transfer from the π moiety to the CH(σ*) moiety (Figure 6), is present,[23] the electron density of the π moiety in the compound, which shows a shielding effect, will be lower than that of the other diastereomeric isomer. Thus, for the nitrogen-containing heteroaromatics, it is possible to observe a differing basicity between the diastereomers.

In fact, we observed a more interesting phenomenon than that expected: each pair of corresponding diastereomers (**3g** and **4g**) derived from (±)-*trans*-2-pyridylcyclohexanol (**1g**) could be effectively separated by extraction with achiral organic media and aqueous acid. That is, partitioning between an organic solvent, such as diethyl ether, and aqueous HCl effectively allowed the separation of the diastereomers (Scheme 3).

It is noteworthy that a pair of diastereomers could be separated by simple extraction with achiral organic media and aqueous acid. Only ether-type nonpolar organic media could be effectively used as the extraction media (Table 4); the



Scheme 3. The separation of the diastereomers by extraction. [a] The kinetic resolution of (±)-**1** was observed in the acylation process when the reaction stopped under the situation remaining unreacted **1**. [b] The indication of "(1*S*, 2*R*)"is depicted by the numbering position of 2-pyridylcyclohexanols before acylation. [c] The ratio used was as follows: a mixture of diastereomers **3** and **4**/aqueous HCl/diethyl ether = 0.3 g:20 mL:50 mL.

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Table 4. Effect of the organic medium versus the extraction ability.

Organic medium	Organic phase		Aqueous phase	
	yield [%]	*de* [%][a]	yield [%]	*de* [%][a]
diethyl ether	73	41 (**3g**)	25	93 (**4g**)
diisopropyl ether	61	64 (**3g**)	36	88 (**4g**)
MTBE	78	33 (**3g**)	19	89 (**4g**)
ethyl acetate	quant.	7 (**3g**)	0	–
toluene	quant.	0	0	–
methylene chloride	quant.	0	0	–

[a] The *de* value was determined by ^{1}H NMR (300 MHz).

suitable amount of ether was ≈40–50 mL for 300 mg of the crude diastereomer mixture (Table 5). It was likely that aqueous HCl was the most suitable aqueous acid in terms of practicality (Table 6 and Scheme 4).

Table 5. Effect of the amount of diethyl ether versus the extraction ability.

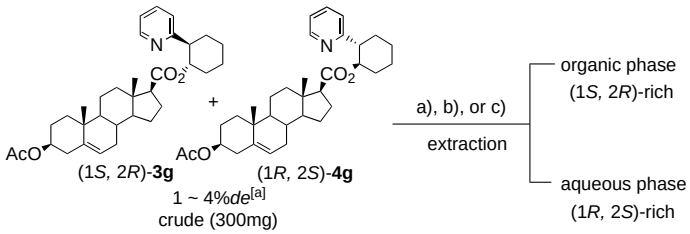
Et_2O [mL]	Organic phase		Aqueous phase	
	yield [%]	*de* [%][a]	yield [%]	*de* [%][a]
20	57	65 (**3g**)	44	76 (**4g**)
40	71	46 (**3g**)	29	89 (**4g**)
50	73	41 (**3g**)	25	93 (**4g**)
60	84	22 (**3g**)	13	94 (**4g**)

[a] The *de* value was determined by ^{1}H NMR (300 MHz).

Table 6. Effect of acid type versus the extraction ability.

Acid [wt %]	Organic phase		Aqueous phase	
	yield [%]	*de* [%][a]	yield [%]	*de* [%][a]
1.0 % HCl	quant.	2 (**3g**)	0	–
2.5 % HCl	88	15 (**3g**)	9	95 (**4g**)
3.0 % HCl	73	41 (**3g**)	25	93 (**4g**)
5.0 % HCl	49	74 (**3g**)	50	57 (**4g**)
50 % AcOH	quant.	0	0	–
3.0 % HBr	70	44 (**3g**)	29	96 (**4g**)

[a] The *de* value was determined by ^{1}H NMR (300 MHz).



Scheme 4. a) The separation of the diastereomers by extraction using various organic media (50 mL) and aqueous HCl (3 %). b) The separation of the diastereomers by extraction with diethyl ether and aqueous HCl (3 %). c) The separation of the diastereomers by extraction with various acids (20 mL) and diethyl ether (50 mL). [a] The kinetic resolution of (±)-**1g** was observed in the acylation process when the reaction stopped under the situation remaining unreacted **1g**.

It is quite interesting to note that the isomer with the aryl-induced ^{1}H NMR signal mostly existed in the organic phase upon extraction (e.g., **3g**: $\delta = 0.12$). We measured each pK_a value of the pyridinium chloride of the corresponding diastereomers and found that these values were quite different (pK_a of 3.81 and 4.15 for **3a** and **4a**, respectively), and the isomer with the aryl-induced shift has a lower pK_a value. These values were determined by the measurement of the dissociation constant by means of the ultraviolet absorption spectrophotometric method at 22 ± 2 °C in aqueous methanol. The measured data are shown in Tables 7 and 8.[26] Equation (1) was used for the calculation of the pK_a value from the absorptiometric curve (261 nm).

$$pK_a = pH + \log\frac{d_B - d}{d - d_A} \quad (1)$$

In Equation (1) d is the absorbance at pH ≈ 3–5, d_A is the absorbance below pH 2 and d_B is the absorbance above pH 7.

Additionally, the X-ray crystallographic analysis of the pure (1*S*, 2*R*) isomer **3i** confirmed the presence of an effective affinity between the C18-CH_3 and π moieties even for the nitrogen-containing heteroaromatics (Figure 7). The C18-

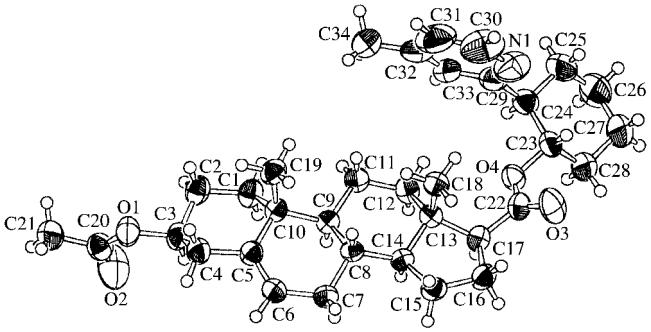


Figure 7. ORTEP drawing of **3i**. ;total energy : 74.32 kcal mol^{-1}.

CH_3 group was found to be in close proximity to the π face of the pyridyl group; this is consistent with the remarkable high-field shift of the C18-CH_3 in the ^{1}H NMR spectrum (Table 3, entry 9).

On the other hand, the (1*R*, 2*S*) isomer **4i**, which did not show an effective aryl-induced ^{1}H NMR shift, was preferentially obtained from the aqueous acid phase. The chemical shift of the C18-CH_3 of the major isomer from the aqueous acid phase showed the lower value of $\delta = 0.46$. Further examples of the separation of the diastereomers derived from various (±)-pyridyl alcohols are shown in Table 9.

The distribution ability was influenced by the concentration of the aqueous acid used, and the optimum concentration of the aqueous HCl was dependent on the structure of mixtures of the diastereomers. In the case of **3g** and **4g**, a 93 % *de* of **4g** was obtained in 25 % yield by concentration of the 3.0 wt % aqueous HCl (pH ≈ 0.02), while 41 % *de* of **3g** was obtained in 73 % yield from the organic layer (Table 9, entry 2). Further extraction of the organic phase (41 % *de*) with 7.0 wt % aqueous HCl improved the *de* of **3a** to 80 % *de* (70 % yield; Scheme 5).

Although we can not provide a clear explanation for this phenomenon at the moment, it can be assumed that the intramolecular CH–π interaction would reduce the electron density of the nitrogen atom on the pyridine ring, as a result of charge-transfer character[23] to CH(σ*) from HOMO of the π

Table 7. Measured data and calculated results for the pK_a value of **3g**.

Measured pH value[a]	Absorbance (d)	d_A, d_B	$d_B - d$	$d - d_A$	$\log(d_B - d)/(d - d_A)$	pK_a[b]
1.31	0.3595	0.3595	–	–	–	–
3.25	0.3185	–	– 0.1455	– 0.0410	0.550	3.80
3.53	0.2939	–	– 0.1209	– 0.0656	0.2655	3.80
3.80	0.2679	–	– 0.0949	– 0.0916	0.015	3.82
4.01	0.2456	–	– 0.0726	– 0.1139	– 0.196	3.81
4.23	0.2233	–	– 0.0503	– 0.1362	– 0.433	3.80
8.09	0.1730	0.1730	–	–	–	–

[a] Measuring apparatus: microbalance: BP-210D (Sartorius AG); pH meter: F-21 (Horiba, Ltd.); spectrophotometer: UV-2400 (Shimadzu Corp.). [b] Average pK_a = 3.81; standard deviation = 0.01.

Table 8. Measured data and calculated results for the pK_a value of **4g**.

Measured pH value[a]	Absorbance (d)	d_A, d_B	$d_B - d$	$d - d_A$	$\log(d_B - d)/(d - d_A)$	pK_a[b]
1.37	0.3898	0.3898	–	–	–	–
3.52	0.3458	–	– 0.1683	– 0.0440	0.583	4.10
3.79	0.3242	–	– 0.1467	– 0.0656	0.3495	4.14
4.03	0.2987	–	– 0.1212	– 0.0911	0.124	4.15
4.25	0.2743	–	– 0.0968	– 0.1155	– 0.077	4.17
4.46	0.2529	–	– 0.0754	– 0.1369	– 0.259	4.20
8.05	0.1775	0.1775	–	–	–	–

[a] The same instruments were used as in Table 7. [b] Average pK_a = 4.15; standard deviation = 0.04.

Table 9. The simple separation of diastereomers (**3** and **4**) by extraction technique.

Entry	R	Concentration of aqueous HCl [wt %]	Organic phase yield [%]	Organic phase *de* [%][a]	Aqueous phase yield [%]	Aqueous phase *de* [%][a]
1	H (**3g** + **4g**)[b]	2.5	88	15 (**3g**)	9	95 (**4g**)
2		3.0	73	41 (**3g**)	25	93 (**4g**)
3		5.0	49	74 (**3g**)	50	57 (**4g**)
4	3-Me (**3h** + **4h**)[c]	1.0	67	29 (**3h**)	27	75 (**4h**)
5		2.0	44	78 (**3h**)	44	73 (**4h**)
6		3.0	31	75 (**3h**)	62	42 (**4h**)
7	4-Me (**3i** + **4i**)[d]	1.0	81	19 (**3i**)	16	88 (**4i**)
8		2.0	56	67 (**3i**)	44	82 (**4i**)
9		3.0	33	73 (**3i**)	63	37 (**4i**)
10	5-Me (**3j** + **4j**)[e]	2.0	97	0	2	68 (**4j**)
11		3.0	61	60 (**3j**)	37	95 (**4j**)
12	6-Me (**3k** + **4k**)[f]	2.0	80	24 (**3k**)	9	93 (**4k**)
13		3.0	59	59 (**3k**)	31	83 (**4k**)
14	4-Cl (**3l** + **4l**)[g]	7.0	97	0	0	–
15		10.0	82	11 (**3l**)	12	55 (**4l**)
16		15.0	42	82 (**3l**)	56	54 (**4l**)

[a] The *de* value was determined by ^{1}H NMR (300 MHz). [b] δ_H of C18-Me; **3g**: 0.115, **4g**: 0.463. [c] δ_H of C18-Me; **3h**: 0.128, **4h**: 0.443. [d] δ_H of C18-Me; **3i**: 0.098, **4i**: 0.464. [e] δ_H of C18-Me; **3j**: 0.136, **4j**: 0.490. [f] δ_H of C18-Me; **3k**: 0.073, **4k**: 0.463. [g] δ_H of C18-Me; **3l**: 0.128, **4l**: 0.479.

moiety, and lead to a decrease in the basicity of the compounds (**3g–l**) as we previously assumed. This interaction has been known as the attractive force which functions even in water.[9e] An alternative possibility is the significant difference in the steric bulkiness around the nitrogen atom in the diastereomers. In any event, these results lead us to the assumption that the difference in the conformation between the diastereomers on the basis of the intramolecular CH–π interaction is an important factor for this phenomenon.

The removal of the steroid moiety gave the optically active pyridyl alcohols in moderate yields (Table 10). Since we have found that the (1*S*, 2*R*) isomer **3** of the diastereomers with an aryl-induced ^{1}H NMR shift has a lower pK_a value and was found to exist in the organic phase upon extraction, this provides a simple and useful method of optically resolving (±)-*trans*-2-pyridylcyclohexanols accompanied by the determination of the absolute configuration (Scheme 6).

Table 10. Removal of steroid moiety from the diastereomer (**3** or **4**).

Diastereomer	*de* of starting diastereomer **3** or **4** [%][a]	Method of reduction[b]	Yield [%]	*ee* of product [%][c]
R = H (**3g**)	81	A	68	77 (1*S*, 2*R*)
R = H (**4g**)	93	A	90	93 (1*R*, 2*S*)
R = Me (**3i**)	67	A	83	64 (1*S*, 2*R*)
R = Me (**4i**)	82	A	90	80 (1*R*, 2*S*)
R = Cl (**3l**)	82	B	70	79 (1*S*, 2*R*)
R = Cl (**3l**)	54	B	89	50 (1*R*, 2*S*)

[a] The *de* value was determined by ^{1}H NMR (300 MHz). [b] Method A: $LiAlH_4$ (10 equiv), THF, RT, 2.0 h; Method B: DIBAL-H (5 equiv), THF, −78 °C, 2.0 h. [c] The *ee* value was determined by HPLC (CHIRALCEL OD, hexane/*i*PrOH = 95:5).

As has been noted, these studies have focused on the cyclic aryl alcohols, such as the (±)-*trans*-2-arylcyclohexanols. However, we examined the other cases by the use of the acyclic-type alcohols and found that the remarkable ^{1}H NMR shifts were also observed in more loosely arranged acyclic aryl alcohols.[27]

The diastereomers (**6** and **7**) were easily obtained from the same reaction of various acyclic (±)-aryl alcohols **5** and acid chloride **2** (Scheme 7).[11] In these cases, the values of the chemical shift in the ^{1}H NMR spectrum of C18-CH_3 on the steroid ring were also apparently different for the diastereomers (Table 11, entries 2–7). One always appeared near δ = 0.5, while the other always appeared near δ = 0.7. We then used compound **5a**, which has a known absolute configura-

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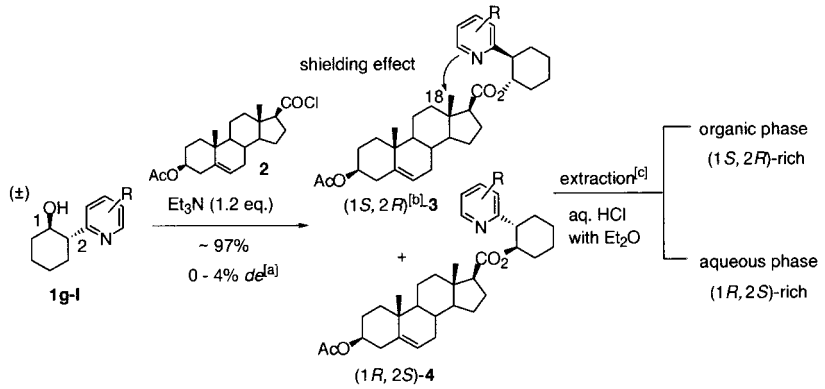
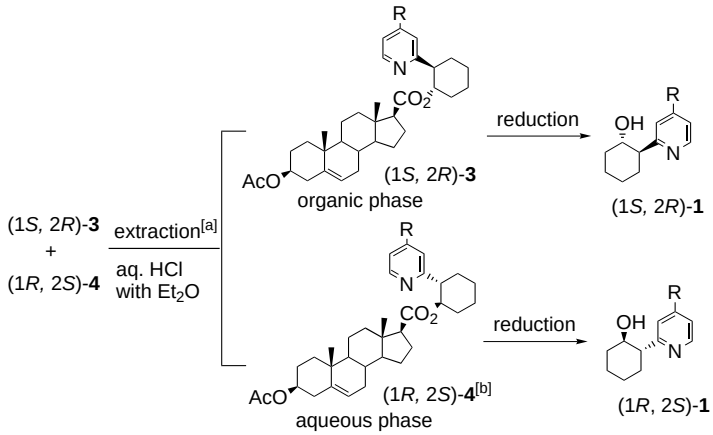
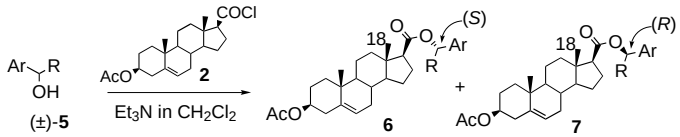


Scheme 5. The separation of the diastereomers of 2-pyridylcyclohexanols (**3** and **4**) by extraction. [a] The kinetic resolution of (±)-**1** was observed in the acylation process when the reaction stopped under the situation remaining unreacted **1**. [b] The indication of "(1*S*, 2*R*)" is depicted by the numbering position of 2-pyridylcyclohexanols before acylation. [c] The ratio used was as follows : a mixture of diastereomers **3** and **4**/aqueous HCl/diethyl ether = 0.3 g:20 mL:50 mL.



Scheme 6. Reduction of the diastereomers to 2-pyridylcyclohexanols. [a] The following ratio was used: a mixture of diastereomers/aqueous HCl/diethyl ether = 0.3 g:20 mL:50 mL. [b] These products were obtained by neutralizing the aqueous phase with $NaHCO_3$ (pH 8).



Scheme 7. Acylation of (±)-**5** with steroid compound **2**.

tion, to clarify which diastereomer showed the shielding effect by the aromatic ring, and found that the diastereomer showing the shielding effect was derived from the *S* alcohol. It is noteworthy that there is almost no exception regarding the chemical shift values in the case of the 1-aryl-1-alkyl alcohols, in spite of the use of various kinds of aromatic moieties (Table 11, entries 1–6). This suggests that this methodology would be a very general method for the determination of the absolute configuration of various analogues. In addition, a similar high-field shift is also observed for the 2-pyridyl alcohols and homoaryl-type alcohols, such as 1-phenylpropan-2-ol (Table 11, entries 7–8).

Similarly, it is probable that the absolute configuration of the 1-aryl-1-alkylamines could be easily determined by this method. Almost the same trends were observed for the 1-aryl-1-alkylamines regarding the absolute configuration and chemical shift value in the ^{1}H NMR spectra. We also found that the diastereomer with the shielding effect was derived from amines bearing the *S* configuration (Table 12, entry 1). Although the yields shown here are isolated yields after column chromatography, it is possible to determine the absolute configurations by the use of crude products without purification, which were obtained in almost quantitative yields (Scheme 8).

Table 11. ^{1}H NMR spectroscopic determination of the absolute configuration of 1-aryl alcohols by means of the CH–π shielding effect

Entry	Ar	R	Yield [%][b]	δ_H of C18-CH_3 in **6** or **7**[a]	Predicted configuration of resolved **5**
1	Ph	Me, **6a**	64	0.51	*S*[c]
		Me, **7a**		0.71	*R*
2	*p*-tolyl	Me, **6b**	74	0.52	*S*
		Me, **7b**		0.71	*R*
3	4-methoxyphenyl	Me, **6c**	77	0.49	*S*
		Me, **7c**		0.70	*R*
4	4-chlorophenyl	Me, **6d**	66	0.51	*S*
		Me, **7d**		0.70	*R*
5	2-naphthyl	Me, **6e**	59	0.52	*S*
		Me, **7e**		0.71	*R*
6	Ph	Et, **6f**	33	0. 48	*S*
		Et, **7f**		0.71	*R*
7	2-pyridyl	Me, **6g**	95	0.59	*S*
		Me, **7g**		0.73	*R*
8	Bn	Me, **6h**	81	0.48	*S*
		Me, **7h**		0.63	*R*

[a] 25 °C in $CDCl_3$. [b] Isolated yields of a mixture of diastereomers by column chromatography. [c] The configuration was confirmed by the use of an enantiomerically pure substrate with known absolute configuration.

Table 12. ^{1}H NMR spectroscopic determination of the absolute configuration of 1-aryl amines by means of the CH–π shielding effect.

Entry	Ar	R	Yield [%][b]	δ_H of C18-CH_3 in **9** or **10**[a]	Predicted configuration of resolved **5**
1	Ph	Me, **9a**	71	0.61	*S*[c]
		Me, **10a**		0.73	*R*
2	*p*-tolyl	Me, **9b**	69	0.62	*S*
		Me, **10b**		0.72	*R*
3	4-bromophenyl	Me, **9c**	78	0.58	*S*
		Me, **10c**		0.71	*R*
4	2-naphthyl	Me, **9d**	68[c]	0.52	*S*[d]
		Me, **10d**	71[c]	0.71	*R*[d]
5	Ph	Et, **9e**	68	0.54	*S*
		Et, **10e**		0.73	*R*

[a] 25 °C in $CDCl_3$. [b] Isolated yields of a mixture of diastereomers by column chromatography. [c] The enantiomerically pure *S* and *R* substrates were used because the racemic substrate is not commercially available. [d] The configuration was confirmed by the use of an enantiomerically pure substrate with known absolute configuration.

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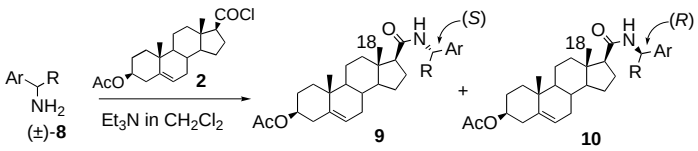

Scheme 8. Acylation of (±)-**8** with steroid compound **2**.

However, in contrast to the 2-arylcyclohexanols, these shielding effects are not very effective from the viewpoint of the extent of the high-field shift in the ^{1}H NMR spectra. The MM calculations[28] of the *S* isomers of **6a** and **7a** suggested the absence of a particularly effective CH – π interaction by the deviation between the π plane and CH moiety, as shown in Figure 8. In addition the *R* isomer **7a** did not completely show the CH – π interaction in the MM calculation.

We presume that this shielding effect was also responsible for the conformational restriction and the attraction of the intramolecular van der Waals force between the CH and π moieties.

In conclusion, the chiral CH – π interaction, which discriminates the environments in two diastereomers in the chiral molecule studied, was found to be a facile tool for the determination of the absolute configuration of various 2-arylcyclohexanols. This strategy is applicable to other acyclic aryl alcohols and amines with high reliability, although in the case of amines, the participation of the intramolecular CH – π interaction remains to be elucidated. The following points are the highlights of this method: 1) a remarkable difference in the shielding effect is observed between the diastereomeric derivatives, 2) the structure of the aryl moiety has no significant influence on the chemical shift value in each series of target molecules and 3) the diastereomeric derivatives have relatively high molecular weight, and can thus be easily handled, even when the amount of the target molecule is low. Needless to say, this methodology can be applied to the determination of the optical purity of various 1-aryl alcohols and amines in a similar manner to the strategy in which chiral shift reagents are used.[29, 30]

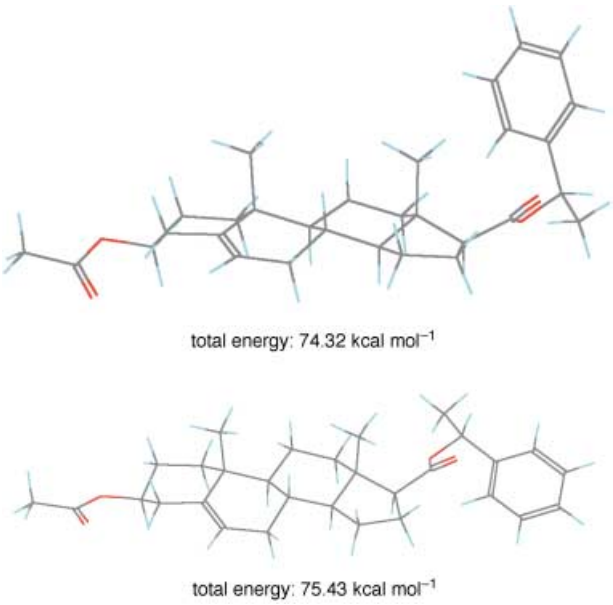

Figure 8. Top: Calculated conformation of *S* isomer **6a**. Total energy: 74.32 kcal mol^{-1}. Bottom: Calculated conformation of *R* isomer **7a**. Total energy: 75.43 kcal mol^{-1}.

In addition, we have shown a novel technique for the optical resolution of (±)-*trans*-pyridyl alcohols by a simple extraction method that employs an achiral organic solvent and an acid solution and makes use of the distribution technique based on a difference in the pK_a values of the diastereomers. We believe that this technique will be able to play an important role in large-scale syntheses and will thus have a high practical value.

Experimental Section

General: Melting points are uncorrected. Infrared (IR) absorption spectra were recorded as a KBr or a NaCl pellet. ^{1}H NMR spectra were measured on 270, 300, 500 or 600 MHz spectrometers with $SiMe_4$ as the internal standard. Specific rotations were measured with a JASCO P-1020 polarimeter. Merck silica gel 60 (70 – 230 mesh ASTM) and Fuji Silysia Chemical silica gel BW-300 were used for column chromatography and flash column chromatography, respectively. (±)-*trans*-2-Arylcyclohexanols[12, 22] (**1b – m**), and acid chloride[11] (**2**) were essentially prepared by the reported method.

(±)-*trans*-2-(4-Methylphenyl)cyclohexanol (1b):[12b] Colourless crystals; m.p. 62 – 62.5 °C (AcOEt/hexane); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.48$ (d, $J = 8.3$ Hz, 1H), 7.15 (m, 3H), 3.65 (m, 1H), 2.33 (s, 3H), 2.13 (m, 2H), 1.34 – 1.87 (m, 7H).

(±)-*trans*-2-(4-Methoxyphenyl)cyclohexanol (1c):[12b] Colourless crystals; m.p. 66.5 – 67 °C (AcOEt/hexane); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.18$ (d, $J = 6.9$ Hz, 2H), 6.88 (d, $J = 6.9$ Hz, 2H), 3.80 (s, 3H), 3.67 (m, 1H), 2.43 (m, 1H), 2.13 (m, 2H), 1.23 – 1.89 (m, 6H).

(±)-*trans*-2-(4-Chlorophenyl)cyclohexanol (1d):[12c] Colourless crystals; m.p. 73 – 73.5 °C (AcOEt/hexane); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.31$ (d, $J = 6.6$ Hz, 2H), 7.19 (d, $J = 6.6$ Hz, 2H), 3.62 (m, 1H), 2.47 (m, 1H), 2.13 (m, 2H), 1.21 – 1.87 (m, 6H).

(±)-*trans*-2-(1-Naphthyl)cyclohexanol (1e):[12b] Colourless crystals; m.p. 127 – 127.5 °C (AcOEt/hexane); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 8.20$ (d, $J = 7.9$ Hz, 1H), 7.87 (d, $J = 2.6$ Hz, 1H), 7.76 (d, $J = 5.6$ Hz, 1H), 7.45 – 7.55 (m, 4H), 3.98 (m, 1H), 3.39 (m, 1H), 2.24 (m, 2H), 1.25 – 1.90 (m, 6H).

(±)-*trans*-2-(2-Naphthyl)cyclohexanol (1f):[12d] Colourless crystals; m.p. 82 – 83 °C (AcOEt/hexane); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.85 – 7.89$ (m, 3H), 7.71 (s, 1H), 7.39 – 7.50 (m, 3H), 3.78 (m, 1H), 2.62 (m, 1H), 2.17 (m, 2H), 1.36 – 1.96 (m, 6H).

Synthesis of 2-(2-pyridyl)cyclohexanones: 2-(2-Pyridyl)cyclohexanones substituted on aromatic ring, which are the precursors of (±)-2-(2-pyridyl)cyclohexanols, were essentially prepared by the reported method.[19a–c]

2-Pyridin-2-ylcyclohexanone:[22a] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.56$ (dd, $J = 5.3$, 1.9 Hz, 0.25H of keto tautomer), 8.32 (d, $J = 4.6$ Hz, 0.75H of enol tautomer), 7.67 (td, $J = 7.8$, 1.8 Hz, 0.75H of enol tautomer), 7.66 (td, $J = 7.7$, 1.9 Hz, 0.25H of keto tautomer), 7.19 – 7.15 (m, 0.5H of keto tautomer), 7.11 (d, $J = 7.8$ Hz, 0.75H of enol tautomer), 7.00 (ddd, $J = 7.8$, 4.6, 0.8 Hz, 0.75H of enol tautomer), 3.84 (dd, $J = 11.2$, 5.9 Hz, 0.25H of keto tautomer), 2.38 – 2.35 (m, 4H), 1.78 – 1.74 (m, 4H), OH of enol tautomer was not observed; IR (KBr): $\tilde{\nu} = 1713$ cm^{-1}.

2-(3-Methylpyridin-2-yl)cyclohexanone: Orange solid; m.p. 56.0 – 57.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.43$ (dd, $J = 4.8$, 0.9 Hz, 1H), 7.44 (dd, $J =$ 7.5, 0.9 Hz, 1H), 7.09 (dd, $J = 7.5$, 4.8 Hz, 1H), 3.91 (dd, $J = 11.7$, 5.8 Hz, 1H), 2.66 – 1.72 (m, 8H), 2.21 (s, 3H); IR (KBr): $\tilde{\nu} = 1713$ cm^{-1}; MS EI(+); *m*/*z* (%): 189 (5) $[M]^+$, 120 (100); HRMS calcd for $C_{12}H_{15}NO$: 189.1154 $[M]^+$; found: 189.1150.

2-(4-Methylpyridin-2-yl)cyclohexanone:[22b] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.41$ (d, $J = 5.0$ Hz, 0.5H), 8.17 (d, $J = 5.2$ Hz,

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0.5H), 6.99 (d, $J = 5.0$ Hz, 0.5H), 6.98 (s, 0.5H), 6.92 (s, 0.5H), 6.83 (d, $J = 5.2$ Hz, 0.5H), 3.81 (dd, $J = 11.4$, 5.9 Hz, 0.5H), 2.75–1.75 (m, 8H), 2.35 (s, 1.5H), 2.34 (s, 1.5H), OH of enol tautomer was not observed; IR (KBr): $\tilde{\nu} = 1715$ cm^{-1}.

2-(5-Methylpyridin-2-yl)cyclohexanone: Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.38$ (dd, $J = 1.5$ and 0.7 Hz, 0.5H), 8.16 (dd, $J = 1.5$ and 0.7 Hz, 0.5H), 7.48 (m, 1H), 7.06 (d, $J = 8.1$ Hz, 0.5H), 7.02 (d, $J = 8.4$ Hz, 0.5H), 3.81 (dd, $J = 11.7$, 5.8 Hz, 0.5H), 2.59–1.73 (m, 8H), 2.31 (s, 1.5H), 2.30 (s, 1.5H), OH of enol tautomer was not observed; IR (KBr): $\tilde{\nu} = 2930$, 1717 cm^{-1}; MS EI(+); m/z (%): 190 (13)$[M+H]^+$, 189 (53) $[M]^+$, 120 (100); HRMS calcd for $C_{12}H_{15}NO$: 189.1154 $[M]^+$; found: 189.1164.

2-(6-Methylpyridin-2-yl)cyclohexanone:[22b] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.56$ (t, $J = 7.8$ Hz, 0.7H of enol tautomer), 7.54 (t, $J = 7.7$ Hz, 0.3H of keto tautomer), 7.02 (d, $J = 7.7$ Hz, 0.3H of keto tautomer), 6.97 (d, $J = 7.7$ Hz, 0.3H of keto tautomer), 6.91 (d, $J = 7.8$ Hz, 0.7H of enol tautomer), 6.84 (d, $J = 7.8$ Hz, 0.7H of enol tautomer), 3.83 (dd, $J = 11.9$, 5.5 Hz, 0.3H of keto tautomer), 2.52 (s, 0.9H of keto tautomer), 2.50 (s, 2.1H of enol tautomer), 2.39–2.32 (m, 3H), 2.15–1.73 (m, 5H), OH of enol tautomer (0.7H) was not observed; IR (KBr): $\tilde{\nu} = 2934$, 1713 cm^{-1}.

2-(4-Chloropyridin-2-yl)cyclohexanone:[22c] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.45$ (d, $J = 6.1$ Hz, 0.38H of keto tautomer), 8.22 (d, $J = 5.6$ Hz, 0.62H of enol tautomer), 7.20–7.19 (m, 0.75H of keto tautomer), 7.10 (d, $J = 1.8$ Hz, 0.62H of enol tautomer), 7.00 (dd, $J = 5.6$ and 1.8 Hz, 0.62H of enol tautomer), 3.82 (dd, $J = 11.8$ and 5.4 Hz, 0.38H of keto tautomer), 2.59–2.31 (m, 4H), 2.17–1.74 (m, 4H), OH of enol tautomer was not observed; IR (KBr): $\tilde{\nu} = 1715$ cm^{-1}.

2-Quinolin-2-ylcyclohexanone:[22a] Orange crystals; m.p. 114.5–116.0 °C (MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.13$ (d, $J = 8.4$ Hz, 0.11H of keto tautomer), 8.03 (d, $J = 8.8$ Hz, 0.11H of keto tautomer), 7.91 (d, $J = 8.3$ Hz, 0.89H of enol tautomer), 7.80 (d, $J = 7.2$ Hz, 0.11H of keto tautomer), 7.71–7.49 (m, 0.33H of keto tautomer), 7.65 (d, $J = 8.6$ Hz, 0.89H of enol tautomer), 7.62 (d, $J = 8.1$ Hz, 0.89H of enol tautomer), 7.58 (ddd, $J = 8.3$, 6.8, 1.5 Hz, 0.89H of enol tautomer), 7.32 (ddd, $J = 8.1$, 6.8 and 1.3 Hz, 0.89H of enol tautomer), 7.16 (d, $J = 8.6$ Hz, 0.89H of enol tautomer), 4.06 (dd, $J = 11.3$ and 6.0 Hz, 0.11H of keto tautomer), 2.48–2.44 (m, 4H), 1.91–1.78 (m, 4H), OH of enol tautomer (0.89H) was not observed; IR (KBr): $\tilde{\nu} = 2932$, 1711 cm^{-1}.

General procedure for the preparation of various (±)-*trans*-2-(2-pyridyl)-cyclohexanols: Small portions of $NaBH_4$ (1.6 g, 43.1 mmol) at 0 °C were added to a stirred solution of 2-(2-pyridyl)cyclohexanone (12.6 g, 71.9 mmol) in EtOH (180 mL). The reaction mixture was refluxed for 2.5 h. The solution was cooled to 0 °C, and more $NaBH_4$ (1.1 g, 28.8 mmol) was added. The reaction mixture was refluxed for a further 1.0 h. After the removal of EtOH under reduced pressure, distilled H_2O was added to the residue at 0 °C. The aqueous mixture was extracted with four portions of $CHCl_3$. The organic layer was washed with brine, dried over Na_2CO_3, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:1) to give **1g** (6.93 g, 55% yield).

(±)-*trans*-2-Pyridin-2-ylcyclohexanol (1g):[22d] Light orange solid; m.p. 59.0–60.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.53$ (d, $J = 4.9$ Hz, 1H), 7.66 (td, $J = 7.5$, 1.9 Hz, 1H), 7.24 (d, $J = 7.5$ Hz, 1H), 7.16 (td, $J = 7.5$, 4.9 Hz, 1H), 4.23 (br, 1H), 3.90 (td, $J = 10.0$, 4.2 Hz, 1H), 2.69 (ddd, $J = 12.2$, 9.5, 3.7 Hz, 1H), 2.09 (m, 2H), 1.83 (m, 2H), 1.62–1.25 (m, 4H); IR (KBr): $\tilde{\nu} = 3326$ cm^{-1}; MS FAB(+); m/z (%): 178 (76) $[M+H]^+$, 154 (100); HRMS calcd for $C_{11}H_{16}NO$: 178.1220 $[M+H]^+$; found: 178.1226.

(±)-*trans*-2-(3-Methylpyridin-2-yl)cyclohexanol (1h): Colourless crystals; m.p. 74.5–75.5 °C (AcOEt/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.40$ (d, $J = 4.6$ Hz, 1H), 7.44 (d, $J = 7.5$ Hz, 1H), 7.05 (dd, $J = 7.5$, 4.6 Hz, 1H), 4.28 (td, $J = 10.0$, 4.1 Hz, 1H), 2.85 (td, $J = 10.4$, 3.4 Hz, 1H), 2.35 (s, 3H), 1.88–1.74 (m, 4H), 1.51–1.36 (m, 4H), 1H of OH was not observed; IR (KBr): $\tilde{\nu} = 3326$ cm^{-1}; MS EI(+); m/z (%): 191 (15) $[M]^+$, 120 (100); HRMS calcd for $C_{12}H_{17}NO$: 191.1310 $[M]^+$; found: 191.1318.

(±)-*trans*-2-(4-Methylpyridin-2-yl)cyclohexanol (1i): Colourless crystals; m.p. 61.5–62.0 °C (Et_2O/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.37$ (d, $J = 5.1$ Hz, 1H), 7.05 (s, 1H), 6.98 (d, $J = 5.1$ Hz, 1H), 3.87 (td, $J = 10.0$, 4.4 Hz, 1H), 2.61 (ddd, $J = 11.9$, 9.6, 3.5 Hz, 1H), 2.34 (s, 3H), 2.12 (br, 1H), 2.03 (m, 2H), 1.82 (m, 2H), 1.53–1.58 (m, 4H); IR (KBr): $\tilde{\nu} = 3326$ cm^{-1}; MS EI(+); m/z (%): 191 (5) $[M]^+$, 120 (100); HRMS calcd for $C_{12}H_{17}NO$: 191.1310 $[M]^+$; found: 191.1310.

(±)-*trans*-2-(5-Methylpyridin-2-yl)cyclohexanol (1j): Colourless crystals; m.p. 63.5–65.0 °C (AcOEt/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.35$ (dd, $J = 1.7$, 0.6 Hz, 1H), 7.47 (dd, $J = 8.0$, 1.7 Hz, 1H), 7.13 (d, $J = 8.0$ Hz, 1H), 4.29 (br, 1H), 3.86 (td, $J = 9.9$, 4.4 Hz, 1H), 2.62 (td, $J = 9.5$, 3.1 Hz, 1H), 2.31 (s, 3H), 2.13 (m, 1H), 2.03 (m, 1H), 1.85–1.78 (m, 2H), 1.51–1.34 (m, 4H); IR (KBr): $\tilde{\nu} = 3281$ cm^{-1}; MS EI(+); m/z (%): 191 (8) $[M]^+$, 120 (100); elemental analysis calcd (%) for $C_{12}H_{17}NO$ (191.3): C 75.35, H 8.96, N 7.32; found: C 75.18, H 8.84, N 7.21.

(±)-*trans*-2-(6-Methylpyridin-2-yl)cyclohexanol (1k): Colourless solid; m.p. 53.5–55.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.55$ (t, $J = 8.0$ Hz, 1H), 7.04 (d, $J = 8.0$ Hz, 1H), 7.01 (d, $J = 8.0$ Hz, 1H), 5.15 (br, 1H), 3.82 (td, $J = 10.5$, 4.2 Hz, 1H), 2.62 (ddd, $J = 10.5$, 3.8, 2.0 Hz, 1H), 2.52 (s, 3H), 2.14–2.06 (m, 2H), 1.84–1.80 (m, 2H), 1.54–1.36 (m, 4H); IR (KBr): $\tilde{\nu} = 3322$ cm^{-1}.

(±)-*trans*-2-(4-Chloropyridin-2-yl)cyclohexanol (1l):[22e] Colourless crystals; m.p. 79.0–80.0 °C (Et_2O/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.42$ (d, $J = 5.3$ Hz, 1H), 7.25 (s, 1H), 7.18 (dd, $J = 5.3$, 1.8 Hz, 1H), 3.89 (td, $J = 10.0$, 4.4 Hz, 1H), 3.80 (br, 1H), 2.64 (ddd, $J = 12.0$, 9.6, 3.6 Hz, 1H), 2.13 (m, 1H), 2.01 (m, 1H), 1.86–1.79 (m, 2H), 1.57–1.34 (m, 4H); IR (KBr): $\tilde{\nu} = 3341$ cm^{-1}.

(±)-*trans*-2-Quinolin-2-ylcyclohexanol (1m):[22c] Yellowish solid; m.p. 129.0–130.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.13$ (d, $J = 8.6$ Hz, 1H), 8.03 (d, $J = 8.4$ Hz, 1H), 7.79 (d, $J = 8.1$ Hz, 1H), 7.70 (td, $J = 7.6$, 1.2 Hz, 1H), 7.51 (t, $J = 7.6$ Hz, 1H), 7.38 (d, $J = 8.4$ Hz, 1H), 4.57 (br, 1H), 4.15 (td, $J = 10.0$, 4.1 Hz, 1H), 2.86 (td, $J = 10.6$, 3.0 Hz, 1H), 2.20–2.17 (m, 2H), 1.89–1.86 (m, 2H), 1.58–1.45 (m, 4H); IR (KBr): $\tilde{\nu} = 3329$ cm^{-1}.

(±)-2-Pyridylethanol (5g):[22g] Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.54$ (dd, $J = 5.0$, 1.8 Hz, 1H), 7.69 (td, $J = 7.7$, 1.8 Hz, 1H), 7.28 (ddd, $J = 7.9$, 0.6, 0.2 Hz, 1H), 7.20 (ddd, $J = 7.5$, 5.0, 0.6 Hz, 1H), 4.90 (q, $J = 6.6$ Hz, 1H), 4.24 (br, 1H), 1.51 (d, $J = 6.6$ Hz, 3H); IR (KBr): $\tilde{\nu} = 3250$ cm^{-1}.

Compound 2:[11] Colourless solid; m.p. 193–195 °C (decomp.); IR: $\tilde{\nu} = 1784$ cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.43$ (m, 1H), 4.81 (m, 1H), 2.88 (m, 1H), 1.98 (s, 3H), 1.06 (s, 3H), 0.83–2.59 (m, 19H), 0.82 (s, 3H).

General procedure for esterification: **1a** (489 mg, 2.77 mmol) at 0 °C was added to a stirred solution of **2** (1.58 g, 4.16 mmol) and Et_3N (0.46 mL, 3.33 mmol) in CH_2Cl_2 (20 mL) under a nitrogen atmosphere. After stirring for 19 h at room temperature, the reaction mixture was washed with water, dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 10:1) to give **3a** and **4a** (1.22 g, 85%) as a diastereomeric mixture.

Mixture of compounds 3a and 4a:

*(1S,2R)-**3a***: Colourless crystals; m.p. 146–147.0 °C (AcOEt/hexane); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.15–7.24$ (m, 5H), 5.32 (m, 1H), 5.05 (dt, 1H, $J = 4.2$, 10.8 Hz), 4.58 (m, 1H), 2.68 (m, 1H), 2.30 (m, 2H), 2.03 (s, 3H), 0.95 (s, 3H), 0.82–2.17 (m, 26H), 0.04 (s, 3H); IR (KBr): $\tilde{\nu} = 1727$ cm^{-1}; elemental analysis calcd (%) for $C_{34}H_{46}O_4$ (518.7): C 78.72, H 8.94; found: C 78.43, H 8.88.

*(1R,2S)-**4a***: Colourless crystals; m.p. 121–121.5 °C (decomp., AcOEt/hexane); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.16–7.23$ (m, 5H). 5.35 (m, 1H), 4.96 (m, 1H), 4.58 (m, 1H), 2.68 (m, 1H), 2.28 (m, 2H), 2.03 (s, 3H), 0.99 (s, 3H), 0.82–2.18 (m, 26H), 0.45 (s, 3H); IR (KBr): $\tilde{\nu} = 1734$ cm^{-1}; elemental analysis calcd (%) for $C_{34}H_{46}O_4$ (518.7): C 78.72, H 8.94; found: C 78.54, H 8.80.

Mixture of compounds 3b and 4b: Colourless solid; m.p. 124–125 °C; IR (KBr): $\tilde{\nu} = 1716$ cm^{-1}; HRMS calcd for $C_{35}H_{48}O_4$: 532.3553 $[M]^+$; found: 532.3556.

(1S,2R*)-**3b***: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.07$ (m, 4H, overlap with signals of the other diastereomer), 5.34 (m, 1H, overlap with signals of the other diastereomer), 4.98 (m, 1H, overlap with signals of the other diastereomer), 4.58 (m, 1H, overlap with signals of the other diastereomer), 2.68 (m, 1H, overlap with signals of the other diastereomer), 2.33 (s, 3H, overlap with signals of the other diastereomer), 2.31–0.84 (m, 28H, overlap with signals of the other diastereomer), 2.04 (s, 3H, overlap with signals of the other diastereomer), 0.95 (s, 3H), 0.07 (s, 3H).

(1R,2S*)-**4b***: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.07$ (m, 4H, overlap with signals of the other diastereomer), 5.34 (m, 1H, overlap with signals of the other diastereomer), 4.98 (m, 1H, overlap with signals of the other

diastereomer), 4.58 (m, 1H, overlap with signals of the other diastereomer), 2.68 (m, 1H, overlap with signals of the other diastereomer), 2.33 (s, 3H, m, 1H, overlap with signals of the other diastereomer), 2.31 – 0.84 (m, 28H, overlap with signals of the other diastereomer), 2.04 (s, 3H, overlap with signals of the other diastereomer), 1.00 (s, 3H), 0.48 (s, 3H).

Mixture of compounds 3c and 4c:

*(1S,2R)-**3c***: Colourless crystals: m.p. 176 – 176.5 °C (Et_2O/hexane); ^1H NMR (270 MHz, $CDCl_3$): $\delta = 7.11$ (d, $J = 8.6$ Hz, 2H), 6.80 (d, $J = 8.6$ Hz, 2H), 5.34 (m, 1H), 4.98 (m, 1H), 4.60 (m, 1H), 3.76 (s, 3H), 2.64 (m, 1H), 2.30 (m, 2H), 2.03 (s, 3H), 0.95 (s, 3H), 0.85 – 2.18 (m, 26H), 0.006 (s, 3H); IR (KBr): $\tilde{\nu} = 1715\ cm^{-1}$; elemental analysis calcd (%) for $C_{35}H_{48}O_5$ (548.8): C 76.61, H 8.82, found: C 76.30, H 8.60; X-ray data: see the Supporting Information.

*(1R,2S)-**4c***: Colourless crystals; m.p. 153 – 154 °C (Et_2O/hexane); ^1H NMR (270 MHz, $CDCl_3$): $\delta = 7.11$ (d, $J = 8.6$ Hz, 2H), 6.80 (d, $J = 8.6$ Hz, 2H), 5.38 (m, 1H), 4.87 (m, 1H), 4.60 (m, 1H), 3.77 (s, 3H), 2.61 (m, 1H), 2.32 (m, 2H), 2.03 (s, 3H), 1.00 (s, 3H), 0.97 – 2.18 (m, 26H), 0.490 (s, 3H); IR (KBr): $\tilde{\nu} = 1732\ cm^{-1}$; X-ray data: see the Supporting Information.

Mixture of compounds 3d and 4d: Colourless solid; m.p. 59 – 60 °C; IR (KBr): $\tilde{\nu} = 1728\ cm^{-1}$; HRMS calcd for $C_{34}H_{45}O_4Cl$: 552.3007 $[M]^+$; found:552.3014 .

(1S,2R*)-**3d***: ^1H NMR (270 MHz, $CDCl_3$): $\delta = 7.24$ (d, $J = 8.6$ Hz, 2H, overlap with signals of the other diastereomer), 7.16 (d, $J = 8.6$ Hz, 2H, overlap with signals of the other diastereomer), 5.34 (m, 1H, overlap with signals of the other diastereomer), 4.98 (m, 1H, overlap with signals of the other diastereomer), 4.61 (m, 1H, overlap with signals of the other diastereomer), 2.68 (m, 1H, overlap with signals of the other diastereomer), 2.32 (m, 2H, overlap with signals of the other diastereomer), 2.29 – 0.81 (m, 26H, overlap with signals of the other diastereomer), 2.04 (s, 3H, overlap with signals of the other diastereomer), 0.97 (s, 3H), 0.12 (s, 3H).

(1R,2S*)-**4d***: ^1H NMR (270 MHz, $CDCl_3$): $\delta = 7.24$ (d, $J = 8.6$ Hz, 2H, overlap with signals of the other diastereomer), 7.16 (d, $J = 8.6$ Hz, 2H, overlap with signals of the other diastereomer), 5.34 (m, 1H, overlap with signals of the other diastereomer), 4.98 (m, 1H, overlap with signals of the other diastereomer), 4.61 (m, 1H, overlap with signals of the other diastereomer), 2.68 (m, 1H, overlap with signals of the other diastereomer), 2.32 (m, 2H), 0.81 – 2.29 (m, 26H, overlap with signals of the other diastereomer), 2.04 (s, 3H, overlap with signals of the other diastereomer), 1.00 (s, 3H), 0.49 (s, 3H).

Mixture of compounds 3e and 4e: Colourless solid; m.p. 139 – 140 °C; IR (KBr): $\tilde{\nu} = 1736\ cm^{-1}$; HRMS calcd for $C_{38}H_{48}O_4$: 568.3553 $[M]^+$; found: 568.3559.

(1S,2R*)-**3e***: ^1H NMR (270 MHz, $CDCl_3$): $\delta = 8.18$ (d, $J = 8.6$ Hz, 1H, overlap with signals of the other diastereomer), 7.81 (d, $J = 8.2$ Hz, 1H, overlap with signals of the other diastereomer), 7.51 (d, $J = 7.9$ Hz, 1H), 7.40 – 7.48 (m, 4H, overlap with signals of the other diastereomer), 5.26 – 5.30 (m, 1H, overlap with signals of the other diastereomer), 5.18 – 5.26 (m, 1H, overlap with signals of the other diastereomer), 4.58 (m, 1H, overlap with signals of the other diastereomer), 3.64 (m, 1H, overlap with signals of the other diastereomer), 2.27 (m, 2H, overlap with signals of the other diastereomer), 2.02 (s, 3H), 0.37 – 1.98 (m, 26H, overlap with signals of the other diastereomer), 0.83 (s, 3H), – 0.21 (s, 3H).

(1R,2S*)-**4e***: ^1H NMR (270 MHz, $CDCl_3$): $\delta = 8.18$ (d, $J = 8.6$ Hz, 1H, overlap with signals of the other diastereomer), 7.81 (d, $J = 8.2$ Hz, 1H, overlap with signals of the other diastereomer), 7.51 (d, $J = 7.9$ Hz, 1H), 7.40 – 7.48 (m, 4H, overlap with signals of the other diastereomer), 5.26 – 5.30 (m, 1H, overlap with signals of the other diastereomer), 5.18 – 5.26 (m, 1H, overlap with signals of the other diastereomer), 4.58 (m, 1H, overlap with signals of the other diastereomer), 3.64 (m, 1H, overlap with signals of the other diastereomer), 2.27 (m, 2H, overlap with signals of the other diastereomer), 2.04 (s, 3H), 0.37 – 1.98 (m, 26H, overlap with signals of the other diastereomer), 0.97 (s, 3H), 0.32 (s, 3H).

Mixture of compounds 3f and 4f:

*(1S,2R)-**3f***: Colourless crystals; m.p. 198 – 199.5 °C (Et_2O/hexane); ^1H NMR (270 MHz, $CDCl_3$): $\delta = 7.73 – 7.81$ (m, 3H), 7.62 (s, 1H), 7.33 – 7.44 (m, 3H), 5.26 (m, 1H), 5.09 (m, 1H), 4.55 (m, 1H), 2.86 (m, 1H), 2.27 (m, 2H), 1.97 (s, 3H), 0.66 – 2.23 (m, 26H), 0.69 (s, 3H), – 0.25 (s, 3H); IR (KBr): $\tilde{\nu} = 1720\ cm^{-1}$; elemental analysis calcd (%) for $C_{38}H_{48}O_4$ (568.8): C 80.24, H 8.51; found: C 79.90, H 8.70; X-ray data: see the Supporting Information.

*(1R,2S)-**4f***: Colourless crystals; m.p. 180 – 181 °C (Et_2O/hexane); ^1H NMR (270 MHz, $CDCl_3$): $\delta = 7.73 – 7.81$ (m, 3H), 7.64 (s, 1H), 7.33 – 7.44 (m, 3H), 5.34 (m, 1H), 5.09 (m, 1H), 4.55 (m, 1H), 2.86 (m, 1H), 2.27 (m, 2H), 2.03 (s, 3H), 0.98 (s, 3H), 0.66 – 2.23 (m, 26H), 0.43 (s, 3H); IR (KBr): $\tilde{\nu} = 1727\ cm^{-1}$.

Mixture of compounds 3g and 4g:

(1S,2R*)-**3g***: Colourless crystals; m.p. 126.0 – 129.0 °C (Et_2O/hexane); $[\alpha]_D^{28} = +22.3$ ($c = 0.63$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.52$ (d, $J = 4.5$ Hz, 1H), 7.57 (td, $J = 7.7$, 1.8 Hz, 1H), 7.18 (d, $J = 7.7$ Hz, 1H), 7.09 (ddd, $J = 7.7$, 4.5, 0.8 Hz, 1H), 5.33 (d, $J = 4.2$ Hz, 1H), 5.24 (td, $J = 10.8$, 4.3 Hz, 1H), 4.58 (m, 1H), 2.91 (td, $J = 11.5$, 3.5 Hz, 1H), 2.31 – 0.84 (m, 28H), 2.03 (s, 3H), 0.95 (s, 3H), 0.11 (s, 3H); IR (KBr): $\tilde{\nu} = 1732\ cm^{-1}$; MS EI(+); *m/z* (%): 519 (3) $[M]^+$, 160 (100); HRMS calcd for $C_{33}H_{45}NO_4$: 519.3348 $[M]^+$; found: 519.3367; elemental analysis calcd (%) for $C_{33}H_{45}NO_4$ (519.7): C 76.26, H 8.73, N 2.70; found: C 76.06, H 8.72, N 2.62.

(1R,2S*)-**4g***: Colourless crystals; m.p. 149.5 – 150.0 °C (Et_2O/hexane); $[\alpha]_D^{28} = -70.7$ ($c = 0.59$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.51$ (d, $J = 4.4$ Hz, 1H), 7.56 (td, $J = 7.7$, 1.8 Hz, 1H), 7.13 (d, $J = 7.7$ Hz, 1H), 7.09 (ddd, $J = 7.7$, 4.4, 0.9 Hz, 1H), 5.34 (d, $J = 4.4$ Hz, 1H), 5.13 (td, $J = 11.0$, 4.2 Hz, 1H), 4.59 (m, 1H), 2.88 (td, $J = 11.0$, 3.6 Hz, 1H), 2.32 – 0.88 (m, 28H), 2.03 (s, 3H), 0.99 (s, 3H), 0.46 (s, 3H); IR (KBr): $\tilde{\nu} = 1732\ cm^{-1}$; MS EI(+); *m/z* (%): 520 (1) $[M+H]^+$, 519 (1) $[M]^+$, 459 (100); HRMS calcd for $C_{33}H_{45}NO_4$: 519.3348 $[M]^+$; found: 519.3358; elemental analysis calcd (%) for $C_{33}H_{45}NO_4$ (519.7): C 76.26, H 8.73, N 2.70; found: C 75.96, H 8.62, N 2.70.

Mixture of compounds 3h and 4h: Colourless solid; m.p. 107.0 – 112.5 °C; IR (KBr): $\tilde{\nu} = 1730\ cm^{-1}$; HRMS calcd for $C_{34}H_{47}NO_4$: 533.3505 $[M]^+$; found: 533.3529.

(1S,2R*)-**3h***: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.39$ (d, $J = 4.6$ Hz, 1H, overlap with signals of the other diastereomer), 7.36 (d, $J = 7.6$ Hz, 1H, overlap with signals of the other diastereomer), 6.97 (dd, $J = 7.6$, 4.6 Hz, 1H, overlap with signals of the other diastereomer), 5.43 – 5.30 (m, 2H), 4.59 (m, 1H, overlap with signals of the other diastereomer), 3.10 (td, $J = 10.8$, 4.0 Hz, 1H), 2.43 – 0.75 (m, 28H, overlap with signals of the other diastereomer), 2.35 (s, 3H), 2.03 (s, 3H, overlap with signals of the other diastereomer), 0.94 (s, 3H), 0.13 (s, 3H).

(1R,2S*)-**4h***: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.39$ (d, $J = 4.6$ Hz, 1H, overlap with signals of the other diastereomer), 7.36 (d, $J = 7.6$ Hz, 1H, overlap with signals of the other diastereomer), 6.97 (dd, $J = 7.6$, 4.6 Hz, 1H, overlap with signals of the other diastereomer), 5.33 (d, $J = 5.0$ Hz, 1H), 5.20 (td, $J = 10.5$, 4.0 Hz, 1H), 4.59 (m, 1H, overlap with signals of the other diastereomer), 3.10 (td, $J = 10.8$, 4.0 Hz, 1H), 2.43 – 0.75 (m, 28H, overlap with signals of the other diastereomer), 2.36 (s, 3H), 2.03 (s, 3H, overlap with signals of the other diastereomer), 0.99 (s, 3H), 0.44 (s, 3H).

Mixture of compounds 3i and 4i:

*(1S,2R)-**3i***: Colourless crystals; m.p. 199.0 – 202.0 °C (AcOEt/hexane); $[\alpha]_D^{29} = +19.2$ ($c = 0.51$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.37$ (d, $J = 5.0$ Hz, 1H), 6.99 (s, 1H), 6.91 (d, $J = 5.0$ Hz, 1H), 5.33 (d, $J = 4.4$ Hz, 1H), 5.22 (td, $J = 10.7$, 4.3 Hz, 1H), 4.58 (m, 1H), 2.86 (td, $J = 11.4$, 3.4 Hz, 1H), 2.30 – 0.84 (m, 28H), 2.30 (s, 3H), 2.03 (s, 3H), 0.95 (s, 3H), 0.10 (s, 3H); IR (KBr): $\tilde{\nu} = 1732$, $1721\ cm^{-1}$; MS EI(+); *m/z* (%): 533 (10) $[M]^+$, 473 (100); HRMS calcd for $C_{34}H_{47}NO_4$: 533.3505 $[M]^+$; found: 533.3499; elemental analysis calcd (%) for $C_{34}H_{47}NO_4$ (533.8): C 76.51, H 8.88, N 2.62; found: C 76.33, H 8.74, N 2.62; X-ray data: see the Supporting Information.

*(1R,2S)-**4i***: Colourless crystals; m.p. 149.0 – 151.0 °C (AcOEt/hexane); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.36$ (d, $J = 4.7$ Hz, 1H), 6.94 (s, 1H), 6.90 (d, $J = 4.7$ Hz, 1H), 5.35 (d, $J = 4.8$ Hz, 1H), 5.11 (td, $J = 10.3$, 4.3 Hz, 1H), 4.59 (m, 1H), 2.84 (td, $J = 11.4$, 3.3 Hz, 1H), 2.30 (s, 3H), 2.21 – 0.88 (m, 28H), 2.03 (s, 3H), 1.00 (s, 3H), 0.46 (s, 3H); IR (KBr): $\tilde{\nu} = 1732\ cm^{-1}$; MS EI(+); *m/z* (%): 533 (4) $[M]^+$, 473 (100); HRMS calcd for $C_{34}H_{47}NO_4$: 533.3505 $[M]^+$; found: 533.3527; elemental analysis calcd (%) for $C_{34}H_{47}NO_4$ (533.8): C 76.51, H 8.88, N 2.62; found: C 76.33, H 8.87, N 2.58.

Mixture of compounds 3j and 4j: Colourless solid; m.p. 112.0 – 118.5 °C; IR (KBr): $\tilde{\nu} = 1728\ cm^{-1}$; HRMS calcd for $C_{34}H_{47}NO_4$: 533.3505 $[M]^+$; found: 533.3507.

(1S,2R*)-**3j***: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.35$ (d, $J = 2.2$ Hz, 1H), 7.38 (dd, $J = 8.1$ and 2.2 Hz, 1H), 7.07 (d, $J = 8.1$ Hz, 1H), 5.33 (d,

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$J = 3.7$ Hz, 1H), 5.18 (td, $J = 10.6$, 4.2 Hz, 1H), 4.58 (m, 1H, overlap with signals of the other diastereomer), 2.88 (td, $J = 11.5$, 3.7 Hz, 1H), 2.31–0.84 (m, 28H, overlap with signals of the other diastereomer), 2.28 (s, 3H, overlap with signals of the other diastereomer), 2.03 (s, 3H, overlap with signals of the other diastereomer), 0.95 (s, 3H), 0.14 (s, 3H).

(1R,2S*)-**4j***: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.34$ (d, $J = 2.4$ Hz, 1H), 7.37 (dd, $J = 7.8$, 2.4 Hz, 1H), 7.02 (d, $J = 7.8$ Hz, 1H), 5.35 (d, $J = 4.4$ Hz, 1H), 5.10 (td, $J = 10.8$, 4.5 Hz, 1H), 4.58 (m, 1H, overlap with signals of the other diastereomer), 2.85 (td, $J = 11.4$, 3.3 Hz, 1H), 2.31–0.84 (m, 28H, overlap with signals of the other diastereomer), 2.28 (s, 3H, overlap with signals of the other diastereomer), 2.03 (s, 3H, overlap with signals of the other diastereomer), 1.00 (s, 3H), 0.49 (s, 3H).

Mixture of compounds 3k and 4k: Colourless solid; m.p. 71.5–75.0 °C; IR (KBr): $\tilde{\nu} = 1730$ cm^{-1}; HRMS calcd for $C_{34}H_{47}NO_4$: 533.3505 $[M]^+$; found: 533.3526.

(1S,2R*)-**3k***: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.46$ (t, $J = 7.7$ Hz, 1H), 6.94 (d, $J = 7.7$ Hz, 2H), 5.33 (d, $J = 3.6$ Hz, 1H), 5.21 (td, $J = 10.8$, 4.2 Hz, 1H), 4.59 (m, 1H, overlap with signals of the other diastereomer), 2.90 (td, $J = 11.6$, 3.8 Hz, 1H), 2.50 (s, 3H, overlap with signals of the other diastereomer), 2.31–0.88 (m, 28H, overlap with signals of the other diastereomer), 2.03 (s, 3H, overlap with signals of the other diastereomer), 0.95 (s, 3H), 0.07 (s, 3H).

(1R,2S*)-**4k***: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.45$ (t, $J = 7.7$ Hz, 1H), 6.99 (d, $J = 7.7$ Hz, 1H), 6.95 (d, $J = 7.7$ Hz, 1H), 5.34 (d, $J = 4.4$ Hz, 1H), 5.12 (td, $J = 10.5$, 4.2 Hz, 1H), 4.59 (m, 1H, overlap with signals of the other diastereomer), 2.88 (td, $J = 11.4$, 3.9 Hz, 1H), 2.50 (s, 3H, overlap with signals of the other diastereomer), 2.31–0.88 (m, 28H, overlap with signals of the other diastereomer), 2.03 (s, 3H, overlap with signals of the other diastereomer), 1.00 (s, 3H), 0.46 (s, 3H).

Mixture of compounds 3l and 4l: Colourless solid; m.p. 61.0–63.0 °C; IR (KBr): $\tilde{\nu} = 1732$ cm$^{-1;}$ MS EI(+); *m/z* (%): 556 (0.2) $[M+2]^+$, 554 (0.6) $[M]^+$, 493 (100); HRMS calcd for $C_{33}H_{44}NO_4Cl$: 553.2968 $[M]^+$; found: 553.2959.

(1S,2R*)-**3l***: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.43$ (d, $J = 5.3$ Hz, 1H), 7.20 (d, $J = 2.0$ Hz, 1H), 7.12 (dd, $J = 5.3$, 2.0 Hz, 1H), 5.34 (m, 1H, overlap with signals of the other diastereomer), 5.19 (td, $J = 10.6$, 4.2 Hz, 1H), 4.58 (m, 1H, overlap with signals of the other diastereomer), 2.86 (m, 1H, overlap with signals of the other diastereomer), 2.31–0.84 (m, 28H, overlap with signals of the other diastereomer), 2.03 (s, 3H, overlap with signals of the other diastereomer), 0.96 (s, 3H), 0.13 (s, 3H).

(1R,2S*)-**4l***: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.42$ (d, $J = 5.1$ Hz, 1H), 7.15 (d, $J = 2.1$ Hz, 1H), 7.12 (dd, $J = 5.1$, 2.1 Hz, 1H), 5.34 (m, 1H, overlap with signals of the other diastereomer), 5.08 (td, $J = 10.4$, 4.2 Hz, 1H), 4.58 (m, 1H, overlap with signals of the other diastereomer), 2.86 (m, 1H, overlap with signals of the other diastereomer), 2.31–0.84 (m, 28H, overlap with signals of the other diastereomer), 2.03 (s, 3H, overlap with signals of the other diastereomer), 1.00 (s, 3H), 0.48 (s, 3H).

Mixture of compounds 3m and 4m: Colourless solid; m.p. 84.0–88.0 °C; IR (KBr): $\tilde{\nu} = 1728$ cm^{-1}; HRMS calcd for $C_{37}H_{47}NO_4$: 569.3505 $[M]^+$; found: 569.3504.

(1S,2R*)-**3m***: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.08$ (d, $J = 7.8$ Hz, 1H, overlap with signals of the other diastereomer), 8.03 (d, $J = 8.5$ Hz, 1H), 7.76 (dd, $J = 8.3$, 0.9 Hz, 1H, overlap with signals of the other diastereomer), 7.67 (ddd, $J = 8.3$, 7.0, 1.5 Hz, 1H), 7.48 (ddd, $J = 7.8$, 7.0, 0.9 Hz, 1H), 7.36 (d, $J = 8.5$ Hz, 1H), 5.32 (m, 1H, overlap with signals of the other diastereomer), 5.26 (m, 1H, overlap with signals of the other diastereomer), 4.55 (m, 1H, overlap with signals of the other diastereomer), 3.17 (td, $J = 11.6$, 3.7 Hz, 1H), 2.31–0.56 (m, 28H, overlap with signals of the other diastereomer), 2.03 (s, 3H, overlap with signals of the other diastereomer), 0.69 (s, 3H), –0.23 (s, 3H).

(1R,2S*)-**4m***: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.08$ (d, $J = 7.8$ Hz, 1H, overlap with signals of the other diastereomer), 8.03 (d, $J = 8.4$ Hz, 1H), 7.76 (dd, $J = 8.3$, 0.9 Hz, 1H, overlap with signals of the other diastereomer), 7.67 (ddd, $J = 8.3$, 6.9, 1.5 Hz, 1H), 7.48 (ddd, $J = 7.8$, 6.9, 0.9 Hz, 1H), 7.31 (d, $J = 8.4$ Hz, 1H), 5.32 (m, 1H, overlap with signals of the other diastereomer), 5.26 (m, 1H, overlap with signals of the other diastereomer), 4.55 (m, 1H, overlap with signals of the other diastereomer), 3.13 (m, 1H), 2.31–0.56 (m, 28H, overlap with signals of the other diastereomer), 2.03 (s, 3H, overlap with signals of the other diastereomer), 0.97 (s, 3H), 0.42 (s, 3H).

Mixture of compounds 6a and 7a:

*(1S)-**6a***: Colourless crystals; m.p. 94–94.5 °C (AcOEt/hexane); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.36$ (d, $J = 6.6$ Hz, 2H), 7.28–7.33 (m, 3H), 5.89 (q, $J = 6.6$ Hz, 1H), 5.37 (m, 1H), 4.60 (m. 1H), 2.35 (m, 2H), 2.03 (s, 3H), 1.53 (d, $J = 6.6$ Hz, 3H), (0.86–2.09 (m, 18H), 0.99 (s, 3H), 0.51 (s, 3H); IR (KBr): $\tilde{\nu} = 1726$ cm^{-1}; HRMS calcd for $C_{30}H_{40}O_4$: 464.2927 $[M]^+$; found: 464.2922.

*(1R)-**7a***: Colourless crystals; m.p. 93–93.5 °C (AcOEt/hexane); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.36$ (d, $J = 7.9$ Hz, 2H), 7.28–7.33 (m, 3H), 5.93 (q, $J = 6.6$ Hz, 1H), 5.38 (m, 1H), 4.60 (m. 1H), 2.35 (m, 2H), 2.04 (s, 3H), 1.54 (d, $J = 6.6$ Hz, 3H), 0.80–2.20 (m, 18H), 1.03 (s, 3H), 0.71 (s, 3H); IR (KBr): $\tilde{\nu} = 1736$ cm^{-1}.

Mixture of compounds 6b and 7b: Amorphous yellow solid; IR (NaCl): $\tilde{\nu} = 1732$ cm^{-1}; HRMS calcd for $C_{31}H_{42}O_4$: 478.3083 $[M]^+$; found: 478.3072.

(1S)-**6b***: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.24$ (d, $J = 7.6$ Hz, 2H, overlap with signals of the other diastereomer), 7.15 (d, $J = 7.6$ Hz, 2H, overlap with signals of the other diastereomer), 5.87 (m, 1H, overlap with signals of the other diastereomer), 5.37 (m, 1H, overlap with signals of the other diastereomer), 4.60 (m. 1H, overlap with signals of the other diastereomer), 2.34 (s, 3H, overlap with signals of the other diastereomer), 2.03 (s, 3H), 1.51 (d, $J = 6.3$ Hz, 3H, overlap with signals of the other diastereomer), 0.74–2.40 (m, 20H, overlap with signals of the other diastereomer), 0.99 (s, 3H), 0.52 (s, 3H).

(1R)-**7b***: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.24$ (d, $J = 7.6$ Hz, 2H, overlap with signals of the other diastereomer), 7.15 (d, $J = 7.6$ Hz, 2H, overlap with signals of the other diastereomer), 5.87 (m, 1H, overlap with signals of the other diastereomer), 5.37 (m, 1H, overlap with signals of the other diastereomer), 4.60 (m. 1H, overlap with signals of the other diastereomer), 2.34 (s, 3H, overlap with signals of the other diastereomer), 2.04 (s, 3H), 1.51 (d, $J = 6.3$ Hz, 3H, overlap with signals of the other diastereomer), 0.74–2.40 (m, 20H, overlap with signals of the other diastereomer), 1.03 (s, 3H), 0.71 (s, 3H).

Mixture of compounds 6c and 7c: Colourless amorphous solid; IR (KBr): $\tilde{\nu} = 1728$ cm^{-1}; HRMS calcd for $C_{31}H_{42}O_5$: 494.3033 $[M]^+$; found: 494.3034.

(1S)-**6c***: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.30$ (d, $J = 8.6$ Hz, 2H, overlap with signals of the other diastereomer), 6.87 (d, $J = 8.6$ Hz, 2H, overlap with signals of the other diastereomer), 5.87 (m, 1 H overlap with signals of the other diastereomer), 5.37 (m, 1H, overlap with signals of the other diastereomer), 4.60 (m. 1H, overlap with signals of the other diastereomer), 3.80 (s, 3H), 2.33 (m, 2H, overlap with signals of the other diastereomer), 2.03 (s, 3H), 1.52 (d, $J = 6.6$ Hz, 3H, overlap with signals of the other diastereomer), 0.93–2.10 (m, 18H, overlap with signals of the other diastereomer), 0.98 (s, 3H), 0.49 (s, 3H).

(1R)-**7c***: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.30$ (d, $J = 8.6$ Hz, 2H, overlap with signals of the other diastereomer), 6.87 (d, $J = 8.6$ Hz, 2H, overlap with signals of the other diastereomer), 5.87 (m, 1H, overlap with signals of the other diastereomer), 5.37 (m, 1H, overlap with signals of the other diastereomer), 4.60 (m. 1H, overlap with signals of the other diastereomer), 3.80 (s, 3H), 2.33 (m, 2H, overlap with signals of the other diastereomer), 2.04 (s, 3H), 1.52 (d, $J = 6.6$ Hz, 3H, overlap with signals of the other diastereomer), 0.93–2.10 (m, 18H, overlap with signals of the other diastereomer), 1.03 (s, 3H), 0.70 (s, 3H).

Mixture of compounds 6d and 7d: Yellow solid; m.p. 52–53 °C; IR (KBr): $\tilde{\nu} = 1736$ cm^{-1}.

(1S)-**6d***: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.31$ (d, $J = 7.2$ Hz, 2H, overlap with signals of the other diastereomer), 7.23 (d, $J = 7.2$ Hz, 2H, overlap with signals of the other diastereomer), 5.88 (m, 1H, overlap with signals of the other diastereomer), 5.38 (m, 1H, overlap with signals of the other diastereomer), 4.58 (m. 1H, overlap with signals of the other diastereomer), 2.32 (m, 2H, overlap with signals of the other diastereomer), 2.03 (s, 3H), 0.85–2.20 (m, 18H, overlap with signals of the other diastereomer), 1.51 (d, $J = 6.6$ Hz, 3H, overlap with signals of the other diastereomer), 0.99 (s, 3H), 0.51 (s, 3H).

(1R)-**7d***: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.31$ (d, $J = 7.2$ Hz, 2H, overlap with signals of the other diastereomer), 7.23 (d, $J = 7.2$ Hz, 2H, overlap with signals of the other diastereomer), 5.88 (m, 1H, overlap with signals of the other diastereomer), 5.38 (m, 1H, overlap with signals of the other

diastereomer), 4.58 (m. 1H, overlap with signals of the other diastereomer), 2.32 (m, 2H, overlap with signals of the other diastereomer), 2.04 (s, 3H), 0.85–2.20 (m, 18H, overlap with signals of the other diastereomer), 1.51 (d, $J = 6.6$ Hz, 3H, overlap with signals of the other diastereomer), 1.03 (s, 3H), 0.70 (s, 3H).

Mixture of compounds 6e and 7e: Colourless solid; m.p. 165–166 °C; IR (KBr): $\tilde{\nu} = 1728$ cm^{-1}; HRMS calcd for $C_{34}H_{42}O_4$: 514.3084 $[M]^+$; found: 515.3152.

(1S)-**6e***: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.80$–7.84 (m, 4H, overlap with signals of the other diastereomer), 7.32–7.48 (m, 3H, overlap with signals of the other diastereomer), 6.17 (m, 1H, overlap with signals of the other diastereomer), 5.38 (m, 1H, overlap with signals of the other diastereomer), 4.61 (m. 1H, overlap with signals of the other diastereomer), 2.02 (s, 3H), 0.72–2.41 (m, 20H, overlap with signals of the other diastereomer), 1.63 (d, $J = 6.3$ Hz, 3H), 0.95 (s, 3H), 0.50 (s, 3H).

(1R)-**7e***: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.80$–7.84 (m, 4H, overlap with signals of the other diastereomer), 7.32–7.48 (m, 3H, overlap with signals of the other diastereomer), 6.17 (m, 1H, overlap with signals of the other diastereomer), 5.38 (m, 1H, overlap with signals of the other diastereomer), 4.61 (m. 1H, overlap with signals of the other diastereomer), 2.03 (s, 3H), 0.72–2.41 (m, 20H, overlap with signals of the other diastereomer), 1.65 (d, $J = 6.3$ Hz, 3H), 1.02 (s, 3H), 0.73 (s, 3H).

Mixture of compounds 6f and 7f: Colourless amorphous solid; IR (NaCl): $\tilde{\nu} = 1747$ cm^{-1}; HRMS calcd for $C_{31}H_{42}O_4$: 478.3083 $[M]^+$; found: 478.3090.

(1S)-**6f***: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.23$–7.36 (m, 5H, overlap with signals of the other diastereomer), 5.66 (m, 1H, overlap with signals of the other diastereomer), 5.36 (m, 1H, overlap with signals of the other diastereomer), 4.60 (m. 1H, overlap with signals of the other diastereomer), 2.33 (m, 2H, overlap with signals of the other diastereomer), 2.15 (m, 2H, overlap with signals of the other diastereomer), 2.03 (s, 3H, overlap with signals of the other diastereomer), 0.81–2.11 (m, 18H, overlap with signals of the other diastereomer), 0.87 (t, $J = 7.3$ Hz, 3H, overlap with signals of the other diastereomer), 0.99 (s, 3H), 0.48 (s, 3H).

(1R)-**7f***: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.23$–7.36 (m, 5H, overlap with signals of the other diastereomer), 5.66 (m, 1H, overlap with signals of the other diastereomer), 5.36 (m, 1H, overlap with signals of the other diastereomer), 4.60 (m. 1H, overlap with signals of the other diastereomer), 2.33 (m, 2H, overlap with signals of the other diastereomer), 2.15 (m, 2H, overlap with signals of the other diastereomer), 2.03 (s, 3H, overlap with signals of the other diastereomer), 0.81–2.11 (m, 18H, overlap with signals of the other diastereomer), 0.87 (t, $J = 7.3$ Hz, 3H, overlap with signals of the other diastereomer), 1.03 (s, 3H), 0.71 (s, 3H).

Mixture of compounds 6g and 7g: Colourless amorphous solid; m.p. 44.5–51.0 °C; IR (KBr): $\tilde{\nu} = 1732$ cm^{-1}.

(1S)-**6g***: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.58$ (ddd, $J = 4.9$, 1.7, 0.9 Hz, 1H), 7.68 (td, $J = 7.7$, 1.7 Hz, 1H), 7.38 (dd, $J = 7.9$, 1.2 Hz, 1H), 7.19 (ddd, $J = 7.5$, 4.9, 1.2 Hz, 1H), 5.93 (q, $J = 6.5$ Hz, 1H), 5.37 (m, 1H), 4.60 (m, 1H, overlap with signals of the other diastereomer), 2.43 (dd, $J = 17.8$ and 9.0 Hz, 1H, overlap with signals of the other diastereomer), 2.33–1.18 (m, 19H, overlap with signals of the other diastereomer), 2.03 (s, 3H, overlap with signals of the other diastereomer), 1.60 (d, $J = 6.5$ Hz, 3H), 1.00 (s, 3H), 0.59 (s, 3H).

(1R)-**7g***: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.57$ (ddd, $J = 4.9$, 1.7 0.9 Hz, 1H), 7.67 (td, $J = 7.7$, 1.7 Hz, 1H), 7.36 (d, $J = 7.9$ Hz, 1H), 7.19 (ddd, $J = 7.5$, 4.9, 1.3 Hz, 1H), 5.95 (q, $J = 6.7$ Hz, 1H), 5.38 (d, $J = 4.2$ Hz, 1H), 4.60 (m, 1H, overlap with signals of the other diastereomer), 2.43 (dd, $J = 17.8$, 9.0 Hz, 1H, overlap with signals of the other diastereomer), 2.33–1.18 (m, 19H, overlap with signals of the other diastereomer), 2.03 (s, 3H, overlap with signals of the other diastereomer), 1.60 (d, $J = 6.7$ Hz, 3H), 1.03 (s, 3H), 0.73 (s, 3H).

Mixture of compounds 6h and 7h: Colourless amorphous solid; IR (KBr): $\tilde{\nu} = 1731$ cm^{-1}; HRMS calcd for $C_{31}H_{42}O_4$: 478.3083 $[M]^+$; found: 478.3063.

(1S*)-6h: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.18$–7.37 (m, 5H, overlap with signals of the other diastereomer), 5.36 (m, 1H, overlap with signals of the other diastereomer), 5.11 (m, 1H, overlap with signals of the other diastereomer), 4.58 (m, 1H, overlap with signals of the other diastereomer), 2.78 (m, 2H), 0.98–2.38 (m, 20H, overlap with signals of the other diastereomer), 2.04 (s, 3H, overlap with signals of the other diastereomer), 1.22 (d, $J = 6.3$ Hz, 3H), 1.00 (s, 3H), 0.48 (s, 3H).

(1R)-**7h***: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.18$–7.37 (m, 5H, overlap with signals of the other diastereomer), 5.36 (m, 1H, overlap with signals of the other diastereomer), 5.11 (m, 1H, overlap with signals of the other diastereomer), 4.58 (m, 1H, overlap with signals of the other diastereomer), 2.92 (m, 2H), 0.98–2.38 (m, 20H, overlap with signals of the other diastereomer), 2.04 (s, 3H, overlap with signals of the other diastereomer), 1.23 (d, $J = 6.3$ Hz, 3H), 1.01 (s, 3H), 0.63 (s, 3H).

Mixture of compounds 9a and 10a

(1S)-9a: Colourless solid; m.p. 73.0–73.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.28$–7.38 (m, 5H), 5.75 (m, 1H), 5.30 (m, 1H), 4.61 (m, 1H), 0.90–2.33 (m, 20H), 2.03 (s, 3H), 1.49 (d, $J = 6.6$ Hz, 3H), 1.00 (s, 3H), 0.61 (s, 3H); IR (KBr): $\tilde{\nu} = 1731$, 1646 cm^{-1}. HRMS calcd for $C_{30}H_{41}NO_3$: 463.3087 $[M]^+$; found: 463.3088.

*(1R)-**10a***: Colourless solid; m.p. 75.0–75.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.24$–7.35 (m, 5H), 5.58 (m, 1H), 5.37 (m, 1H), 4.62 (m, 1H), 0.94–2.37 (m, 20H), 2.04 (s, 3H), 1.50 (d, $J = 6.6$ Hz, 3H), 1.03 (s, 3H), 0.73 (s, 3H); IR (KBr): $\tilde{\nu} = 1732$, 1646 cm^{-1}.

Mixture of compounds 9b and 10b: Colourless solid; m.p. 77.0–78.0 °C; IR (KBr): $\tilde{\nu} = 1734$, 1645 cm^{-1}.

(1S)-**9b***: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.21$ (d, $J = 7.9$ Hz, 2H), 7.14 (d, $J = 7.9$ Hz, 2H), 5.50 (d, $J = 7.9$ Hz, 1H), 5.36 (m, 1H), 5.12 (q, $J = 7.3$ Hz, 1H), 4.60 (m, 1H), 2.03 (s, 3H), 0.82–2.39 (m, 20H), 1.63 (s, 3H), 1.47 (d, $J = 6.9$ Hz, 3H), 1.00 (s, 3H), 0.62 (s, 3H).

(1R)-**10b***: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.25$ (d, $J = 7.9$ Hz, 2H), 7.15 (d, $J = 7.9$ Hz, 2H), 5.51 (m, 1H), 5.36 (m, 1H), 5.39 (m, 1H), 5.16 (m, 1H), 4.63 (m, 1H), 2.03 (s, 3H), 0.85–2.46 (m, 20H), 1.72 (s, 3H), 1.48 (d, $J =$ 6.9 Hz, 3H), 1.03 (s, 3H), 0.72 (s, 3H).

Mixture of compounds 9c and 10c: Colourless solid; m.p. 68.5–69.5 °C; IR (KBr): $\tilde{\nu} = 1732$, 1648 cm^{-1}; HRMS calcd for $C_{30}H_{40}NO_3Br$: 541.2192 $[M]^+$; found: 541.2193.

(1 S)-**9c***: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.44$ (d, $J = 8.6$ Hz, 2H), 7.21 (d, $J = 8.6$ Hz, 2H), 5.84 (d, $J = 7.6$ Hz, 1H), 5.36 (m, 1H), 5.09 (m, 1H), 4.60 (m, 1H), 2.32 (m, 2H), 0.97–2.27 (m, 18H), 2.04 (s, 3H), 1.45 (d, $J = 6.9$ Hz, 3H), 1.01 (s, 3H), 0.58 (s, 3H).

(1R)-**10c***: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.44$ (d, $J = 8.6$ Hz, 2H), 7.21 (d, $J = 8.6$ Hz, 2H), 5.49 (m, 1H), 5.40 (m, 1H), 5.17 (m, 1H), 4.60 (m, 1H), 0.97–2.30 (m, 18H), 2.05 (s, 3H), 1.47 (d, $J = 6.6$ Hz, 3H), 1.03 (s, 3H), 0.71 (s, 3H).

Mixture of compounds 9d and 10d:

*(1S)-**9d***: Colourless solid; m.p. 133.5–134.0 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.80$–7.84 (m, 4H), 7.44–7.49 (m, 3H), 5.59 (d, $J = 7.9$ Hz, 1H), 5.37 (m, 1H), 5.34 (m, 1H), 4.59 (m, 1H), 0.90–2.34 (m, 20H), 2.01 (s, 3H), 1.58 (d, $J = 6.9$ Hz, 3H), 0.99 (s, 3H), 0.62 (s, 3H); IR (KBr): $\tilde{\nu} =$ 1728 cm^{-1}.

*(1R)-**10d***: Colourless solid; m.p. 135.0–135.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.76$–7.84 (m, 4H), 7.43–7.49 (m, 3H), 5.56 (d, $J = 7.9$ Hz, 1H), 5.38 (m, 1H), 5.35 (m, 1H), 4.67 (m, 1H), 0.90–2.38 (m, 20H), 2.04 (s, 3H), 1.60 (d, $J = 6.9$ Hz, 3H), 1.03 (s, 3H), 0.75 (s, 3H); IR (KBr): $\tilde{\nu} = 1736$, 1658 cm^{-1}.

Mixture of compounds 9e and 10e: Pale yellow solid; m.p. 78.5–79.5 °C; IR (KBr): $\tilde{\nu} = 1736$, 1652 cm^{-1}; HRMS calcd for $C_{31}H_{43}NO_3$: 477.3243 $[M]^+$; found: 477.3241.

(1S)-**9e***: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.23$–7.36 (m, 5H, overlap with signals of the other diastereomer), 5.54 (m, 1H, overlap with signals of the other diastereomer), 5.37 (m, 1H, overlap with signals of the other diastereomer), 4.91 (m, 1H, overlap with signals of the other diastereomer), 4.59 (m, 1H, overlap with signals of the other diastereomer), 0.91–2.32 (m, 20H, overlap with signals of the other diastereomer), 2.05 (s, 3H, overlap with signals of the other diastereomer), 1.83 (m, 2H, overlap with signals of the other diastereomer), 0.99 (s, 3H), 0.89 (m, 3H, overlap with signals of the other diastereomer), 0.54 (s, 3H).

(1R)-**10e***: ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.23$–7.36 (m, 5H, overlap with signals of the other diastereomer), 5.54 (m, 1H, overlap with signals of the other diastereomer), 5.37 (m, 1H, overlap with signals of the other diastereomer), 4.91 (m, 1H, overlap with signals of the other diastereomer), 4.59 (m, 1H, overlap with signals of the other diastereomer), 0.91–2.32 (m, 20H, overlap with signals of the other diastereomer), 2.05 (s, 3H, overlap with signals of the other diastereomer), 1.83 (m, 2H, overlap with

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signals of the other diastereomer), 1.03 (s, 3H), 0.89 (m, 3H, overlap with signals of the other diastereomer), 0.73 (s, 3H).

General procedure for extraction: Aqueous 3.0 wt% HCl (20 mL, diluted 36% HCl with dist. H_2O) was added to a solution of **3g** and **4g** (300 mg, 1:1 mixture of diastereomers) in diethyl ether (50 mL). After vigorous shaking, the ethereal solution was separated from the aqueous layer, dried over Na_2CO_3 and filtered. The filtrate was concentrated in vacuo to give **3g** in 73% yield with 41% *de*. The aqueous layer was made alkaline with $NaHCO_3$ (pH 8) to precipitate a white solid. The precipitate was collected by suction filtration and dried to give **4g** in 25% yield with 93% *de*.

Procedure for the reduction of ester 3c: To a stirred solution of **3c** (112 mg, 0.204 mmol) in dry THF (3 mL) was added $LiAlH_4$ (78 mg, 2.05 mmol) at room temperature. After 1 h, the reaction mixture was treated by successive dropwise addition of 78 mL of water, 78 mL of 15% sodium hydroxide solution, and 234 mL of water. After filtration of the granular precipitate, the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt 2:1) to give (1*S*, 2*R*)-**1c** (42 mg, 99.8%) as colourless crystals.

(1*S*,2*R*)-*trans*-2-(4-Methoxyphenyl)cyclohexanol[12b] **(1c)**: Colourless solid; m.p. 66–67 °C; $[\alpha]_D^{30} = +26.0$ ($c = 0.908$, $CHCl_3$); 99% *ee* [The *ee* was determined by HPLC analysis (Daicel Chiralcel OJ; hexane/*i*PrOH = 99:1; flow rate: 1.0 mL min^{-1}; 25 °C; t_R 43.0 min.)]; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.18$ (m, 2H), 6.88 (m, 2H), 3.80 (s, 3H), 3.61 (m, 1H), 2.29 (m, 1H), 2.11 (m, 1H), 1.26–1.89 (m, 8H).

(1*R*,2*S*)-*trans*-2-(4-Methoxyphenyl)cyclohexanol (1c):[12b] Colourless solid; m.p. 68–69 °C; 99% *ee* [The *ee* was determined by HPLC analysis (Daicel Chiralcel OJ; hexane/*i*PrOH = 99:1; flow rate: 1.0 mL min^{-1}; 25 °C; t_R 46.0 min.)]; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 7.18$ (m, 2H), 6.88 (m, 2H), 3.80 (s, 3H), 3.61 (m, 1H), 2.29 (m, 1H), 2.11 (m, 1H), 1.26–1.89 (m, 8H).

(1*S,2*R**)-*trans*-2-Pyridin-2-ylcyclohexanol (1g)**: White solid; m.p. 64.0–64.5 °C; $[\alpha]_D^{28} = +20.4$ ($c = 0.49$, $CHCl_3$); 77% *ee* [The *ee* was determined by HPLC analysis (Daicel Chiralcel OD; hexane/*i*PrOH = 95:5); flow rate: 1.0 mL min^{-1}; 25 °C; t_R 9.9 min.]].

(1*R,2*S**)-*trans*-2-Pyridin-2-ylcyclohexanol (1g)**: White solid; m.p. 64.5–65.5 °C; $[\alpha]_D^{27} = -23.5$ ($c = 0.53$, $CHCl_3$); 93% *ee* [The *ee* was determined by HPLC analysis (Daicel Chiralcel OD; hexane/*i*PrOH = 95:5; flow rate: 1.0 mL min^{-1}; 25 °C; t_R 13.2 min.)].

(1*S*,2*R*)-*trans*-2-(4-Methylpyridin-2-yl)cyclohexanol (1i): White crystals; m.p. 65.0–66.0 °C; $[\alpha]_D^{27} = +17.0$ ($c = 0.53$, $CHCl_3$); 64% *ee* [The *ee* was determined by HPLC analysis (Daicel Chiralcel OD; hexane/*i*PrOH = 95:5; flow rate: 1.0 mL min^{-1}; 25 °C; t_R 8.9 min.)].

(1*R*,2*S*)-*trans*-2-(4-Methylpyridin-2-yl)cyclohexanol (1i): White crystals; m.p. 64.0–65.0 °C; $[\alpha]_D^{29} = -24.8$ ($c = 0.56$, $CHCl_3$); 80% *ee* [The *ee* was determined by HPLC analysis (Daicel Chiralcel OD; hexane/*i*PrOH = 95:5; flow rate: 1.0 mL min^{-1}; 25 °C; t_R 10.3 min.)].

(1*S,2*R**)-*trans*-2-(4-Chloropyridin-2-yl)cyclohexanol (1l)**: White solid; m.p. 75.5–76.5 °C; $[\alpha]_D^{28} = +30.6$ ($c = 0.92$, $CHCl_3$); 79% *ee* [The *ee* was determined by HPLC analysis (Daicel Chiralcel OD; hexane/*i*PrOH = 95:5; flow rate: 1.0 mL min^{-1}; 25 °C; t_R 8.4 min.)].

(1*R,2*S**)-*trans*-2-(4-Chloropyridin-2-yl)cyclohexanol (1l)**: White solid; m.p. 77.0–78.0 °C; $[\alpha]_D^{28} = -20.5$ ($c = 0.72$, $CHCl_3$); 50% *ee* [The *ee* was determined by HPLC analysis (Daicel Chiralcel OD; hexane/*i*PrOH = 95:5; flow rate: 1.0 mL min^{-1}; 25 °C; t_R 9.7 min.)].

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