

Supplementary Information

An enantiopure imidazole with cyclophane-type planar chirality

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(ii) General

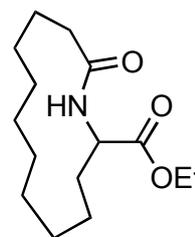
¹H and ¹³C NMR spectra were recorded on a Varian Mercury 300 operating at 300 and 75 MHz, respectively. IR spectra were recorded on a Jasco model FT/IR-480plus. EI-MS spectra were recorded on a Shimadzu GCMS-QP5000 on a positive mode. X-Ray data were corrected on a Rigaku/MSC Mercury diffractometer with graphite monochromated Mo K α radiation. Analytical high performance liquid column chromatography (HPLC) experiments were performed on a Jasco PU-980 intelligent HPLC pump equipped with a UV-975 intelligent UV/Vis detector. Preparative HPLC experiments were performed using a Japan Analytical Industry model LC-918 equipped with a variable-wavelength UV/vis detector.

Tetrahydrofuran was distilled from sodium wire and benzophenone before use. *N,N*-Dimethylformamide was dried over P₂O₁₀, distilled from CaH₂, and stored over activated molecular sieves. 2-(Ethoxycarbonyl)cyclododecanone (**6**) was synthesized from cyclododecanone (**5**) according to the method in a literature (J. A. Marshall and V. H. Audia, *J. Org. Chem.* 1987, **52**, 1106–1113). Other chemicals were used as received.

(iii) Experimental procedure for the synthesis of **1**, **6**, **7**, and **8**

Ethyl 13-oxo-azacyclotridecane-2-carboxylate (7):

Methanesulfonic acid (41 mL, 632 mmol) was added to a chloroform solution (200 mL) of 2-(ethoxycarbonyl)cyclododecanone (**6**, 18.86 g, 74.1 mmol) at 0 °C. To the solution was slowly added sodium azide (13.65 g, 210 mmol) in several portions in a period of 1.5 h at 0 °C with stirring. The resultant mixture was stirred at rt for 1 h, diluted with chloroform (70 mL), and brought to reflux. After being stirred under reflux for 4 h and then at rt overnight, the resultant mixture was poured into crashed ice/water (500 mL) and treated with 28 wt% aqueous ammonia (*ca.* 50 mL) until pH of the aqueous layer became 9–10. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 x 100 mL). Organic layers combined were dried over anhydrous MgSO₄ and concentrated under reduced pressure. The resultant residue was diluted with chloroform (50 mL) and allowed to stand overnight at 4 °C to afford a white precipitate. The solid was filtered off, and the filtrate was concentrated under reduced pressure and then subjected to crystallization from ethyl acetate to give **7** (8.90 g, 33.0 mmol, 45%) as a white solid.

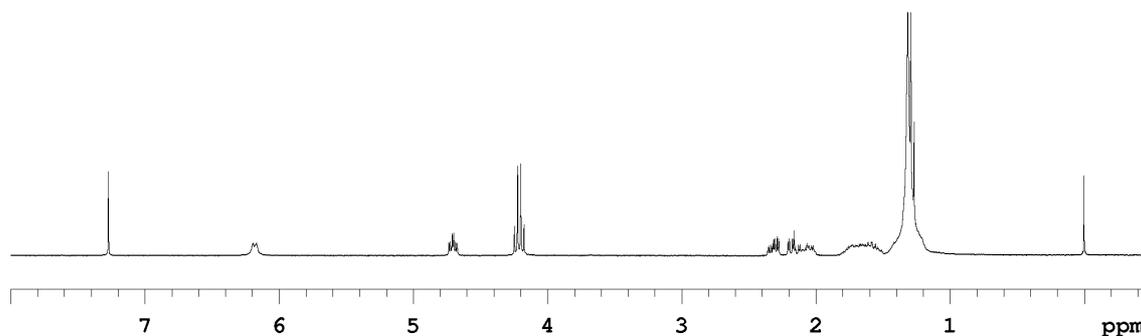


7

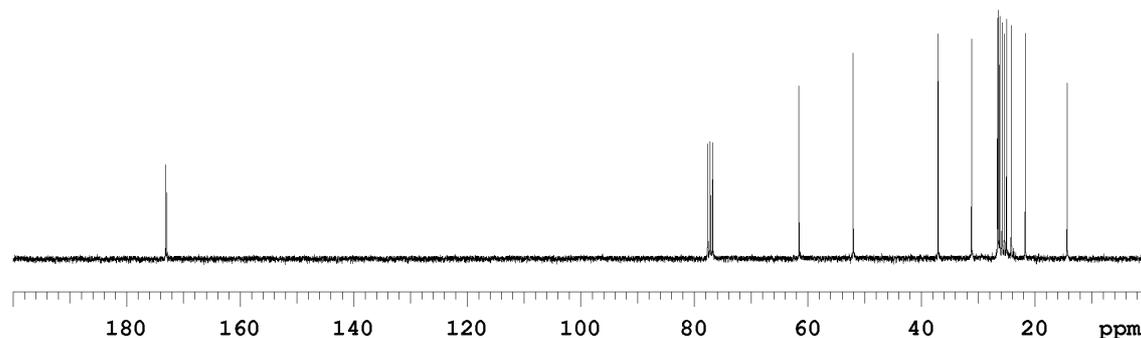
IR (KBr) ν 3315, 2934, 2859, 1748, 1637, 1540, 1459, 1444, 1377, 1223, 1023 cm⁻¹.

EI-MS calcd for [M]⁺ C₁₅H₂₇NO₃ = 269, found 269.

¹H NMR (CDCl₃) δ 1.25–2.36 (2H, m), 1.29 (3H, t), 4.21 (2H, q, *J* = 7.2 Hz), 4.70 (1H, m), 6.12 (1H, broad d, *J* = 7.2 Hz).

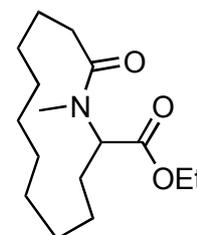


¹³C NMR (CDCl₃) δ 14.29, 21.67, 24.14, 24.97, 25.33, 25.74, 26.17, 26.46, 26.57, 31.13, 37.03, 51.99, 61.54, 173.07.

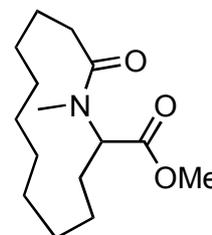


Ethyl 1-methyl-13-oxo-azacyclotridecane-2-carboxylate (S1):

To an *N,N*-dimethylformamide solution (10 mL) of **7** (1.00 g, 3.71 mmol) and methyl iodide (1.0 mL, 16.1 mmol) was added sodium hydride (197 mg, 4.51 mmol, 55% oil dispersion) at 0 °C. After being stirred at the temperature for 30 min and then at rt overnight, the resultant mixture was diluted with water (100 mL) and extracted with dichloromethane (3 x 50 mL). Organic layers combined were concentrated to a volume of *ca.* 20 mL, washed with water (3 x 70 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure to dryness. The resultant residue was subjected to silica gel column chromatography eluted with ethyl acetate/hexane (1:4, v/v) to give **S1** (819 mg, 2.89 mmol, 78%) as a colorless oil and its methyl ester analogue **S2** (88.9 mg, 0.33 mmol, 9%) as a colorless oil. According to the NMR study, **S1** and **S2** were found to exist as a mixture of two conformers.



S1

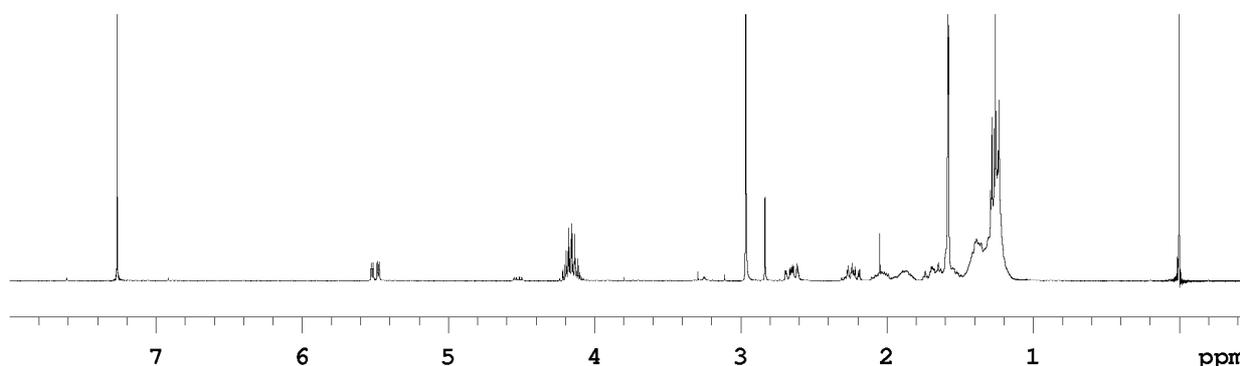


S2

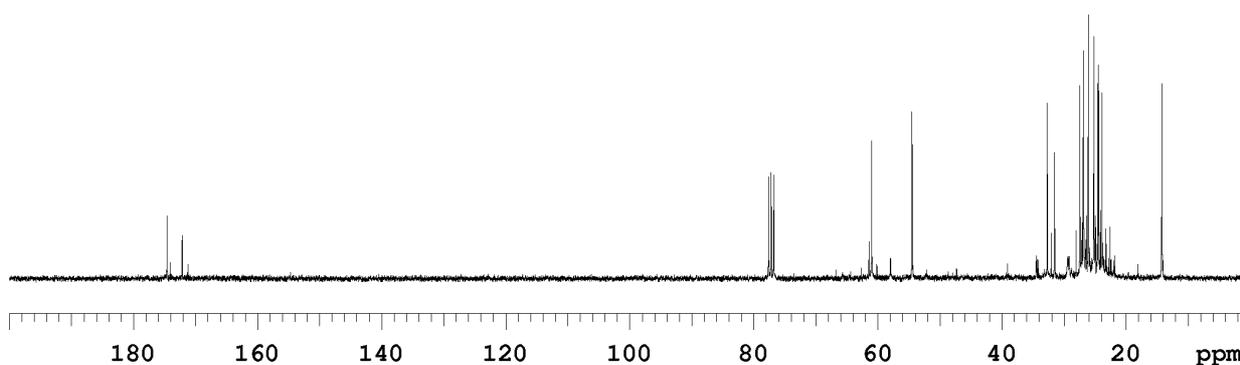
IR (NaCl) ν 3362, 2930, 2861, 1737, 1645, 1027 cm⁻¹.

EI-MS calcd for [M]⁺ C₁₆H₂₉NO₃ = 283, found 283.

¹H NMR (CDCl₃, two conformers) δ 1.23–2.69 (23H, m), 2.83 and 2.96 (3H, s x 2), 4.08–4.24 (2H, m), 4.52 and 5.50 (1H, dd x 2, *J* = 4.5 and 11.0 Hz and *J* = 3.9 and 12.3 Hz).

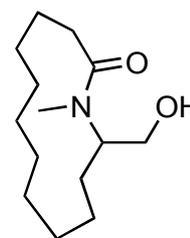


¹³C NMR (CDCl₃, the major conformer) δ 14.20, 23.82, 24.39, 24.48, 25.12, 24.16, 26.07, 26.81, 26.86, 27.40, 31.47, 32.66, 54.46, 60.97, 172.12, 174.56.



13-Hydroxymethyl-1-methylazacyclotridecan-2-one (8):

A mixture of **S1** and **S2** (**S1** 2.89 mmol; **S2** 0.033 mmol) was dissolved in tetrahydrofuran. To the solution was added lithium chloride (428 mg, 10.0 mmol), and the mixture was cooled to $-10\text{ }^{\circ}\text{C}$. To the mixture were successively added sodium tetrahydroborate (380 mg, 10.0 mmol) and ethanol (7.5 mL). After being stirred at the temperature for 30 min, the mixture was allowed to warm to rt. After being stirred at the temperature overnight, the resultant mixture was poured into an aqueous citric acid (10 wt%, 125 mL) and extracted with ethyl acetate (3 x 50 mL). Organic layers combined were successively washed with water (3 x 100 mL) and brine (100 mL), dried over anhydrous MgSO_4 , and volatiles were removed under reduced pressure to give **8** as a colorless oil (453 mg, 1.88 mmol, 94%). According to the NMR study, **8** was found to exist as a mixture of three conformers.

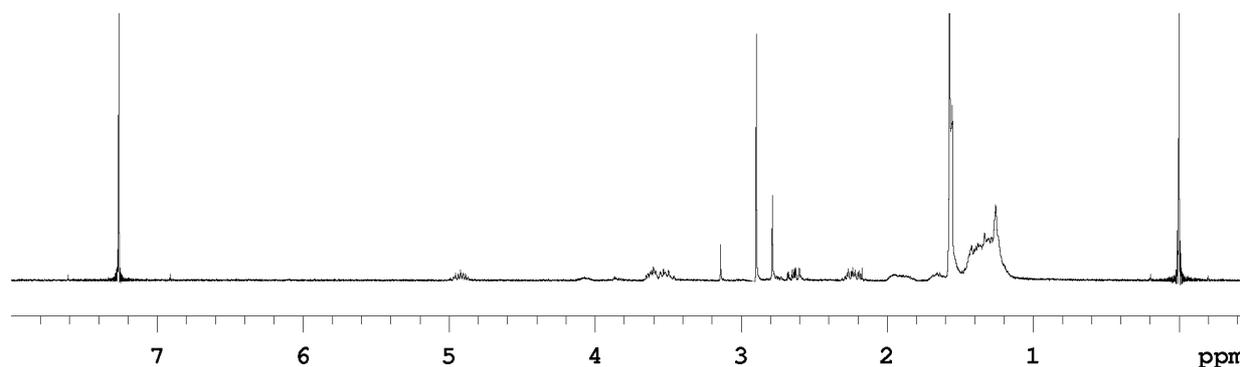


8

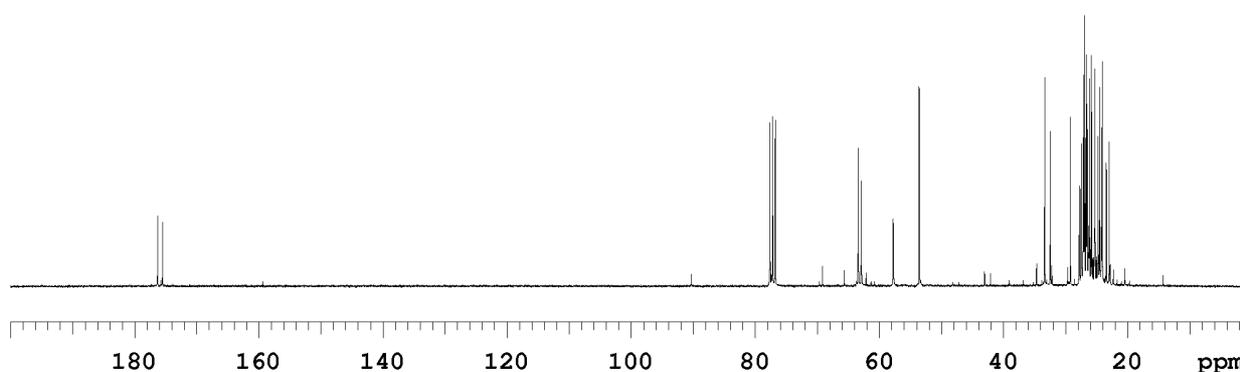
IR (NaCl) ν 3389, 2928, 2860, 1739, 1614 cm^{-1} .

EI-MS calcd for $[\text{M}]^+$ $\text{C}_{14}\text{H}_{27}\text{NO}_2 = 241$, found 241.

^1H NMR (CDCl_3 , three conformers) δ 1.26–2.78 (23H, m), 2.79, 2.90 and 3.14 (3H, s x 3), 4.87–4.99, 3.80–3.88 and 4.00–4.13 (1H, m x 3).

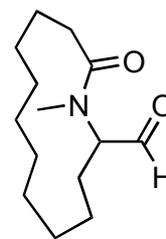


^{13}C NMR (CDCl_3 , the major two conformers) δ 22.93, 23.38, 24.04, 24.16, 24.46, 24.72, 25.20, 25.25, 25.78, 26.10, 26.22, 26.46, 26.55, 26.66, 26.88, 27.03, 27.12, 27.45, 27.74, 29.18, 32.42, 33.32, 53.55, 57.73, 62.90, 63.36, 175.46, 176.29.



1-Methyl-13-oxo-azacyclotridecane-2-carbaldehyde (S3):

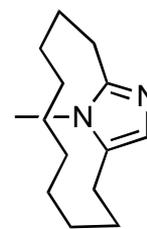
A dichloromethane solution (80 mL) of oxalyl chloride (3.0 mL, 34.9 mmol) was cooled to $-78\text{ }^{\circ}\text{C}$, and dimethyl sulfoxide (5.0 mL, 70.4 mmol) was added dropwise to the solution in a period of 8 min. The mixture was stirred for 15 min, and a dichloromethane solution (50 mL) of **8** (4.08 g, 16.9 mmol) was added dropwise to the mixture in a period of 2 h. After being stirred at the temperature for 30 min, triethylamine (12 mL, 86.3 mmol) was added dropwise to the mixture in a period of 15 min. The resultant mixture was stirred at the temperature for 15 min, allowed to warm to rt, stirred at rt for 60 min, poured into an aqueous solution of citric acid (10 wt%, 80 mL), and extracted with dichloromethane (3 x 80 mL). Organic layers combined were successively washed with a saturated aqueous solution of sodium hydrogencarbonate (200 mL), water (200 mL), and brine (200 mL), dried over anhydrous MgSO_4 , and concentrated under reduced pressure to give a crude mixture containing **S3** as a yellow oil (4.57 g). Because **S3** was found to be unstable at rt, further purification and characterization was not conducted.



S3

2,5-Decamethylene-1-methylimidazole (*rac*-1a):

A crude mixture containing **S3** (4.57 g), obtained as described above, and ammonium acetate (30.7 g, 400 mmol) were dissolved in acetic acid (100 mL). The solution was purged with argon and stirred at 100 °C for 1 h. Then, the reaction mixture was allowed to cool to rt, poured to crashed ice/water (100 mL), treated with a 28 wt% aqueous ammonia (80 mL), and extracted with ethyl acetate (3 x 100 mL). Organic layers combined were dried over anhydrous MgSO₄ and concentrated under reduced pressure. The resultant residue was subjected to silica gel column chromatography (eluted with chloroform/methanol = 100:0 to 97:3 (v/v) to afford *rac*-**1a** (2.45 g, 11.1 mmol, 66%, two steps from **8**) as a white solid.



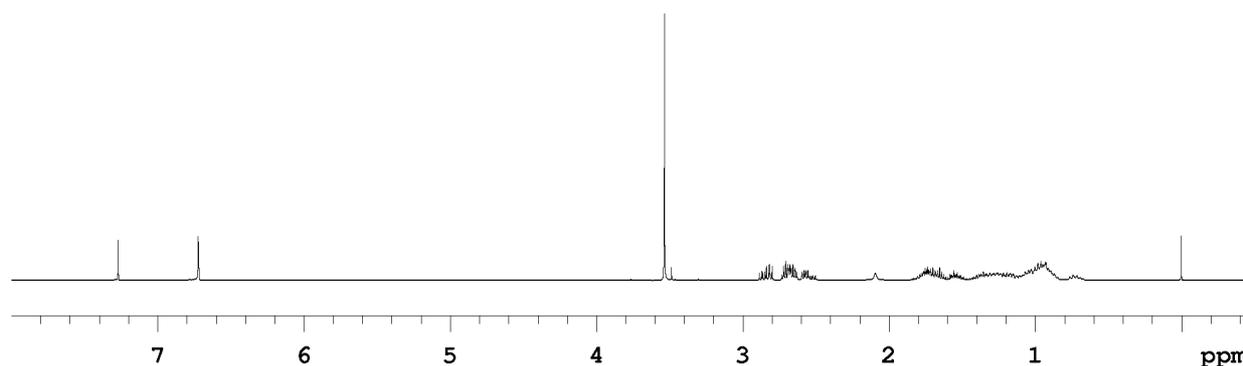
***rac*-1a**

IR (NaCl) ν 2925, 2856, 1683, 1496, 1459, 1404, 1270, 1115, 1120, 1074, 1025, 957, 887, 806 cm⁻¹.

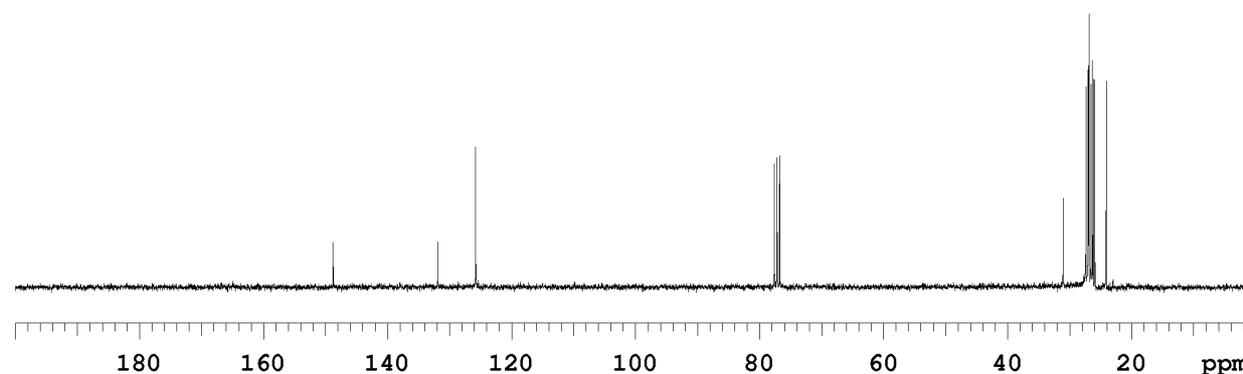
EI-MS calcd for [M]⁺ C₁₄H₂₄N₂ = 220, found 220.

Anal. calcd for C₁₄H₂₄N₂, C: 76.12 H: 11.09 N: 12.52, found C: 76.31 H: 10.98 N: 12.71.

¹H NMR (CDCl₃) δ 0.64–1.85 (16H, m), 2.50–2.73 (3H, m), 2.80–2.89 (1H, m), 3.53 (3H, s), 6.72 (1H, s).

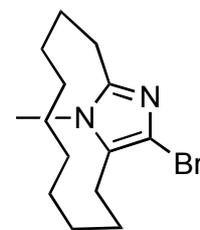


¹³C NMR (CDCl₃) δ 24.07, 25.89, 26.15, 26.28, 26.51, 26.85, 26.90, 26.99, 27.33, 31.00, 125.75, 131.84, 148.73.



4-Bromo-2,5-decamethylene-1-methylimidazole (*rac*-1b):

To a tetrahydrofuran solution (19 mL) of *rac*-1a (1.46 g, 6.61 mmol) was added *N*-bromosuccinimide (1.18 g, 6.61 mmol) at 0 °C. After being stirred at the temperature for 2 h, the resultant mixture was concentrated under reduced pressure, diluted with an aqueous solution of KOH (0.3 M, 30 mL), and extracted with ethyl acetate (2 x 30 mL). The organic layers combined were successively washed with water (50 mL) and brine (50 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography eluted with chloroform to afford *rac*-1b as a white solid (939 mg, 5.42 mmol, 82%).

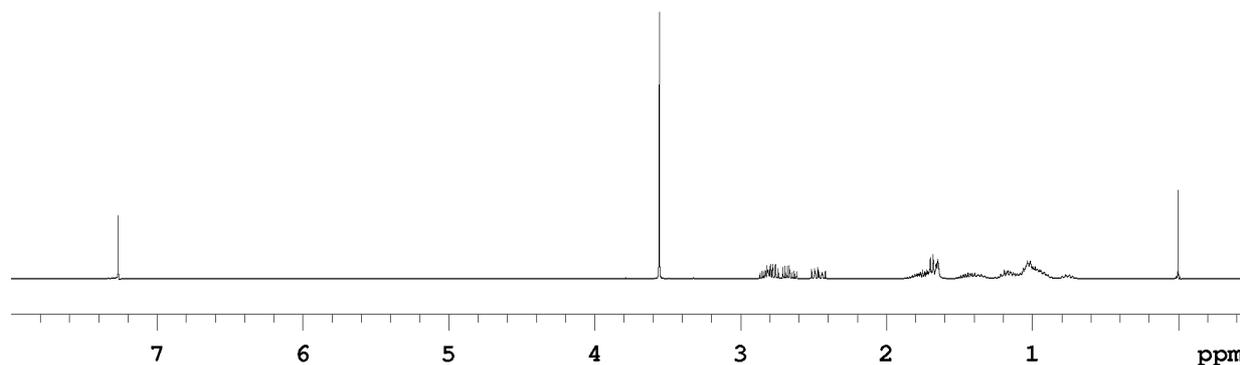


***rac*-1b**

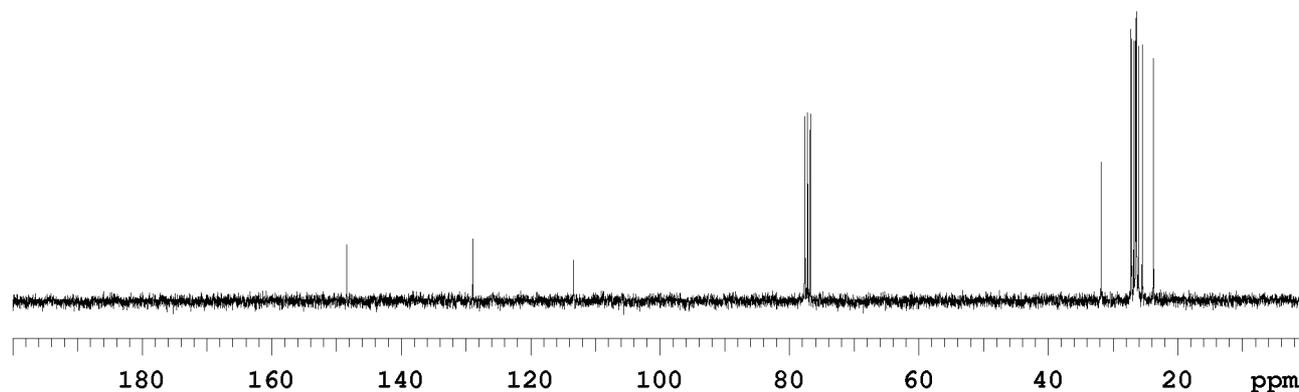
IR (NaCl) ν 2926, 2857, 1558, 1495, 1460, 1401, 1230, 1141, 1091, 1031, 985, 885 cm⁻¹.

EI-MS calcd for [M]⁺ C₁₄H₂₃BrN₂ = 298, found 298.

¹H NMR (CDCl₃) δ 0.64–1.85 (16H, m), 2.50–2.73 (3H, m), 2.80–2.89 (1H, m), 3.53 (3H, s), 6.72 (1H, s).

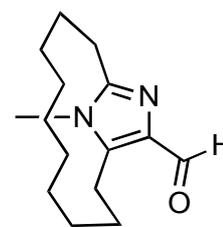


¹³C NMR (CDCl₃) δ 23.71, 25.44, 26.03, 26.29, 26.38, 26.44, 26.51, 26.75, 27.09, 27.19, 31.81, 113.32, 128.89, 148.36.



2,5-Decamethylene-4-formyl-1-methylimidazole (*rac*-1c):

To a diethyl ether solution (3.0 mL) of *rac*-1b was added a hexane solution of butyllithium (1.6 M, 265 μ L, 0.42 mmol) at -78 °C with stirring. The mixture was stirred at the temperature for 1 h, and then *N,N*-dimethylformamide (270 μ L, 3.50 mmol) was added. The mixture was allowed to warm to rt and stirred for 11 h. After treatment with water (10 mL), the mixture was extracted with ethyl acetate (3 x 10 mL). Organic layers combined were washed with brine (15 mL), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The resultant residue was subjected to silica gel column chromatography eluted with chloroform/methanol (100:0 to 98:2, v/v) to afford *rac*-1c as a colorless oil (64.6 mg, 0.26 mmol, 74%).

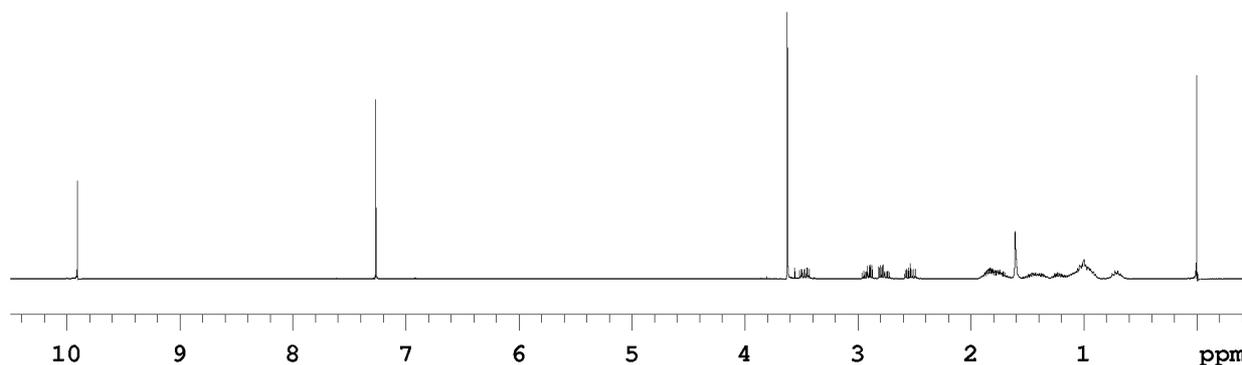


***rac*-1c**

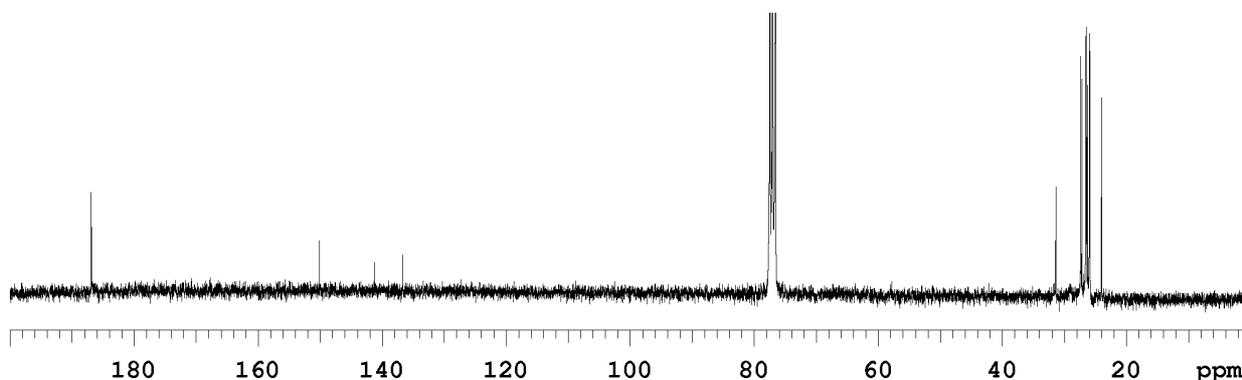
IR (NaCl) ν 2928, 2857, 1675, 1556, 1506, 1460, 1360, 1315, 907, 805 cm^{-1} .

EI-MS calcd for $[\text{M}]^+$ $\text{C}_{15}\text{H}_{24}\text{NO} = 248$, found 248.

$^1\text{H-NMR}$ (CDCl_3) δ 0.65–0.77 (1H, m), 0.90–1.90 (15H, m), 2.49–2.58 (1H, m), 2.72–2.81 (1H, m), 2.87–2.96 (1H, m), 3.43–3.51 (1H, m), 3.63 (3H, s), 9.91 (1H, s).

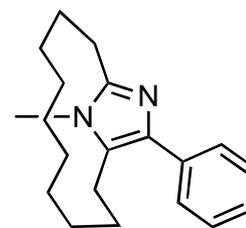


$^{13}\text{C NMR}$ (CDCl_3) δ 23.98, 25.82, 25.86, 25.92, 26.23, 26.38, 26.45, 26.52, 27.14, 27.32, 136.62, 141.24, 150.07, 186.87.



2,5-Decamethylene-1-methyl-5-phenylimidazole (*rac*-1d):

A toluene solution (2.5 mL) of *rac*-1b (149.6 mg, 0.50 mmol) was purged with argon. To the solution was successively added palladium tetrakis(triphenylphosphine) (35.13 mg, 30 μ mol), an ethanol solution (1.5 mL) of phenylboronic acid (96.4 mg, 0.80 mmol), and an aqueous solution of Na₂CO₃ (2.0 M, 0.6 mL, 1.3 mmol). After being refluxed for 36 h, the mixture was extracted with dichloromethane (3 x 5 mL). Organic layers combined were concentrated under reduced pressure, and the residue was subjected to preparative TLC developed with chloroform/methanol/acetic acid (85:10:5, v/v/v) to give a crude mixture containing *rac*-1d. For further purification, the mixture was diluted with dichloromethane (10 mL), successively washed with an aqueous solution of KOH (1.0 M, 5 mL) and brine (10 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure. The resultant residue was subjected to preparative TLC developed with chloroform/methanol (95:5, v/v) to give *rac*-1d as a white waxy oil (90.7 mg, 0.31 mmol, 61% yield).

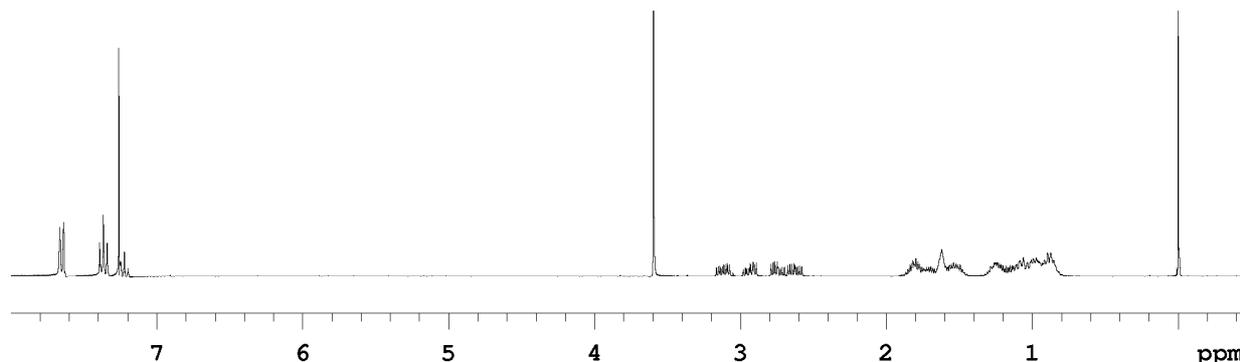


***rac*-1d**

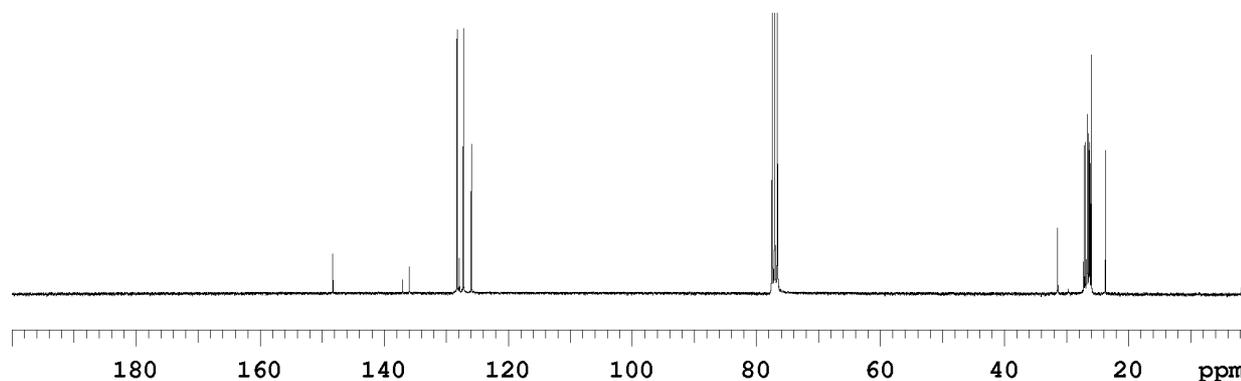
IR (NaCl) ν 2926, 2857, 1602, 1517, 1460, 1402, 1336, 1260, 1071, 1022, 799, 771, 698 cm⁻¹.

EI-MS calcd for [M]⁺ C₂₀H₂₈N₂ = 296, found 296.

¹H-NMR (CDCl₃) δ 0.82–1.91 (16H, m), 2.58–2.79 (2H, m), 2.89–2.98 (1H, m), 3.05–3.16 (1H, m), 3.60 (3H, s), 7.19–7.26 (1H, m), 7.34–7.39 (2H, m), 7.64–7.67 (2H, m).

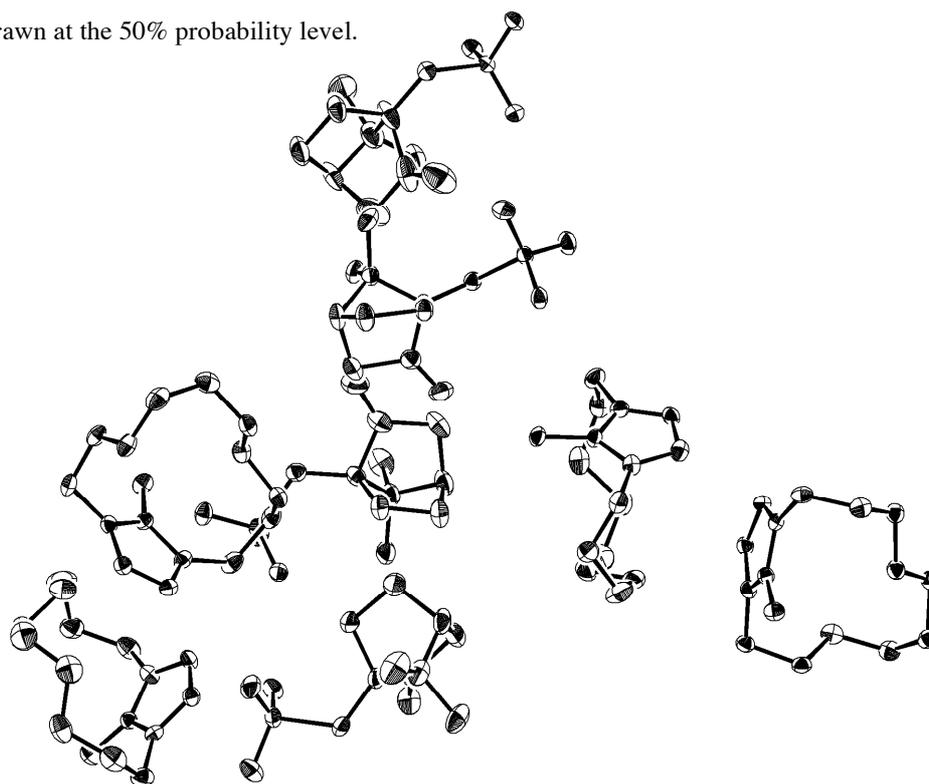


¹³C NMR (CDCl₃) δ 23.67, 25.95, 26.18, 26.28, 26.41, 26.61, 26.65, 26.93, 27.15, 31.38, 125.92, 127.22, 127.85, 128.22, 135.92, 137.01, 148.24.



(iv) X-Ray crystal structure of the salt of (S)-1a with (+)-10-camphorsulfonic acid

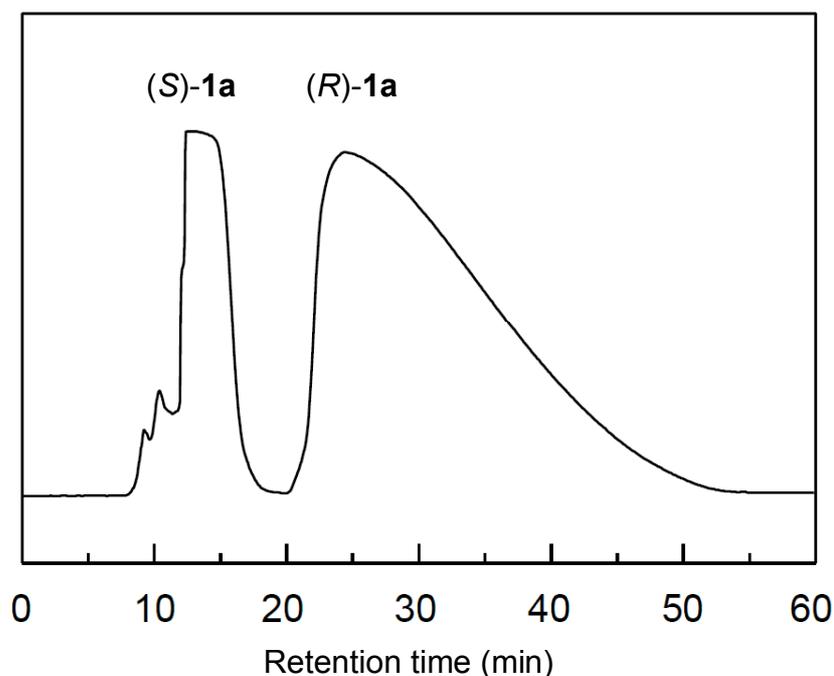
Ellipsoids are drawn at the 50% probability level.



Empirical formula	C ₂₄ H ₄₀ N ₂ O ₄ S	
Formula weight	452.64	
Temperature	103(2) K	
Wavelength	0.71070 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 23.772(3) Å b = 14.7346(13) Å c = 30.466(5) Å	α = 90°. β = 112.7064(18)°. γ = 90°.
Volume	9844(2) Å ³	
Z	16	
Density (calculated)	1.222 Mg/m ³	
Absorption coefficient	0.163 mm ⁻¹	
F(000)	3936	
Crystal size	0.80 x 0.80 x 0.50 mm ³	
Theta range for data collection	1.66 to 25.00°.	
Index ranges	-27 ≤ h ≤ 28, -13 ≤ k ≤ 17, -36 ≤ l ≤ 28	
Reflections collected	26938	
Independent reflections	13396 [R(int) = 0.0400]	
Completeness to theta = 25.00°	99.6 %	
Max. and min. transmission	0.9230 and 0.8807	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	13396 / 1 / 1129	
Goodness-of-fit on F ²	1.018	
Final R indices [I > 2σ(I)]	R1 = 0.0481, wR2 = 0.1331	
R indices (all data)	R1 = 0.0515, wR2 = 0.1388	
Absolute structure parameter	0.01(5)	
Largest diff. peak and hole	1.251 and -0.393 e.Å ⁻³	

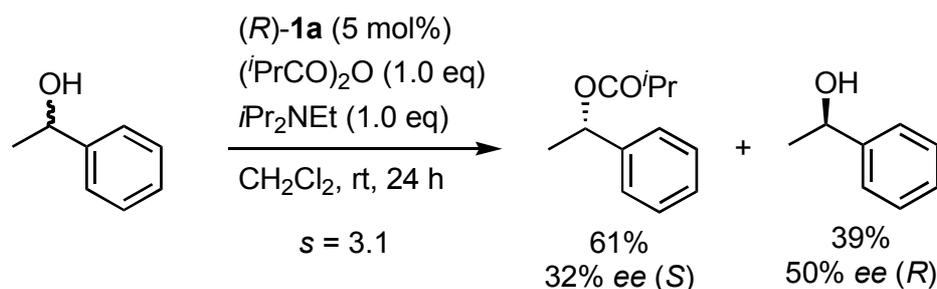
(v) Resolution of *rac*-**1a** by preparative chiral HPLC

A hexane/2-propanol solution (67:33, v/v, 1.0 mL) of *rac*-**1** (0.50 g) was subjected to preparative chiral HPLC. Conditions: column, Daicel Chiralcel OD-H (20 × 250 mm); eluent, hexane/2-propanol = 67:33, v/v; flow rate, 6.0 mL/min; detection, UV absorption at 233 nm. The fractions with the retention time of 10–18 min (f1) and 21–50 min (f2) were concentrated under reduced pressure to give (*S*)- and (*R*)-**1a**, respectively, in quantitative yields.



The enantiomeric purity of the two fractions was confirmed to be >99.5% ee by analytical HPLC. Conditions: column, Daicel Chiralcel OD-H (4 × 250 mm); eluent, hexane/2-propanol = 90:10, v/v; flow rate, 1.0 mL/min; detection, UV absorption at 230 nm; retention time, 8.4 min ((*S*)-**1a**) and 26.9 min ((*R*)-**1a**).

(v) Kinetic resolution of 1-phenylethanol catalyzed by (*R*)-1a



N,N-Diisopropylethylamine (25.8 mg, 34 μ L, 200 μ mol), 1-phenylethanol (25.0 mg, 200 μ mol), (*R*)-1a (2.2 mg, 10 μ mol), and 2-methylpropanoic anhydride (31.6 mg, 33 μ L, 200 μ mol) were dissolved in deuterated chloroform (500 μ L). The mixture was left to stand at rt, and the conversion of the alcohol to the ester was monitored by measuring the ¹H NMR spectra of the solution. After 24 h, 61% conversion of the alcohol to the ester was confirmed by a ¹H NMR analysis, and the reaction mixture was diluted with dichloromethane (0.5 mL) and successively washed with aqueous solution of HCl (1.0 M, 3 x 2 mL) and saturated aqueous solution of NaHCO₃ (2 x 2 mL). The organic layer was concentrated under reduced pressure to give a mixture of the alcohol and the ester as a colorless oil.

The enantiomeric excesses of the alcohol and the ester thus obtained were estimated by chiral HPLC. Conditions: column, Daicel Chiralcel OB-H (4 x 250 mm); eluent, hexane/2-propanol = 90:10, v/v; flow rate, 1.0 mL/min; detection, UV absorption at 254 nm; retention time, 4.45 min ((*R*)-ester), 5.49 min ((*S*)-ester), 6.74 min ((*S*)-alcohol), and 9.13 min ((*R*)-alcohol).

