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Convenient synthesis of an enantiomerically pure bicyclic proline and its *N*-oxyl derivatives

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ABSTRACT

An enantiomerically pure bicyclic proline derivative was prepared by *cis*-selective allylation and diastereospecific intramolecular alkylation starting from D-pipecolinic acid. In addition, enantiomerically pure azabicyclo *N*-oxyls derived from the bicyclic proline worked well as catalysts for the enantioselective electrooxidation of racemic *sec*-alcohols to afford optically active *sec*-alcohols in moderate enantiomeric purity.

1. Introduction

Recently, the importance of quaternary α-amino acids and their peptides has continued to increase in the fields of medicinal chemistry and protein engineering.[1] Since quaternary α-amino acids are non-proteinogenic, their synthesis has attracted considerable attention.[2] Among them, bicyclic proline analogues **A** bridged at the 2nd and 5th carbons of the pyrrolidine ring have unique biological[3] and conformational[4] properties. Therefore, several synthetic methods for their preparation have been developed (Fig. 1).[5] However, to the best of our knowledge, the synthesis of enantiomerically enriched bicyclic proline **A1** with an 8-azabicyclo[3.2.1]octane skeleton has not been accomplished to date.[6] Herein, we report a convenient method for the synthesis of **A1**[7] starting from D-pipecolinic acid. In addition, chiral *N*-oxyls derived from **A1** were prepared and used for the enantioselective electrooxidation of DL-1-phenylethanol.[8]

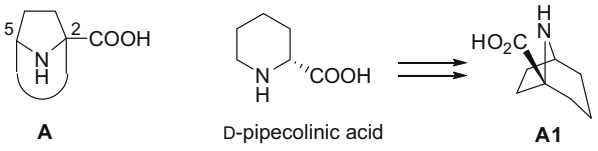


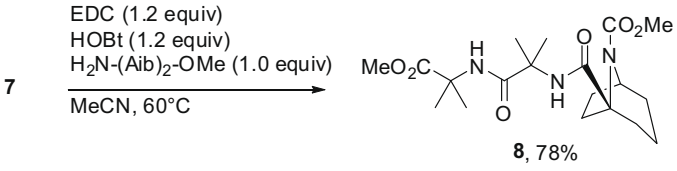
Figure 1. Structure of bicyclic proline analogue **A**.

2. Results and discussion

2.1. Synthesis of bicyclic proline derivative 6

Our strategy for synthesis of bicyclic proline derivative **6** is shown in Scheme 1, which consists of *cis*-selective allylation and diastereospecific intramolecular alkylation. To start with, electrochemical methoxylation[9] of D-pipecolinic acid derivative **1** afforded 6-methoxypipecolinate **2**, which was allylated with allyltrimethylsilane catalyzed by BF_3–OEt_2 to give diastereomerically enriched 6-allylated pipecolinate *cis*-**3**.[10] After isolation of *cis*-**3** by chromatography, transformation of the 6-allyl group into a tosyloxyethyl group was carried out by ozonolysis and then by $NaBH_4$ reduction followed by tosylation to obtain **5** in sufficiently high yield. Finally, compound **5** underwent a base-catalyzed intramolecular alkylation[5d,11] to afford enantiomerically pure **6** with an 8-azabicyclo[3.2.1]octane skeleton in high yield. Further alkaline hydrolysis of **6** gave *N*-protected bicyclic proline **7** in quantitative yield.

The stereochemistry of **6** was determined by X-ray crystallographic analysis after derivatization of **7** to heterotripeptide **8**.[12] The transformation was carried out via a solution-phase method, employing 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt) as coupling reagents (Eq. 1). As shown in Figure 2, the bicyclic proline analogue has conformational properties similar to those of proline, which is a β-turn inducer.[13]



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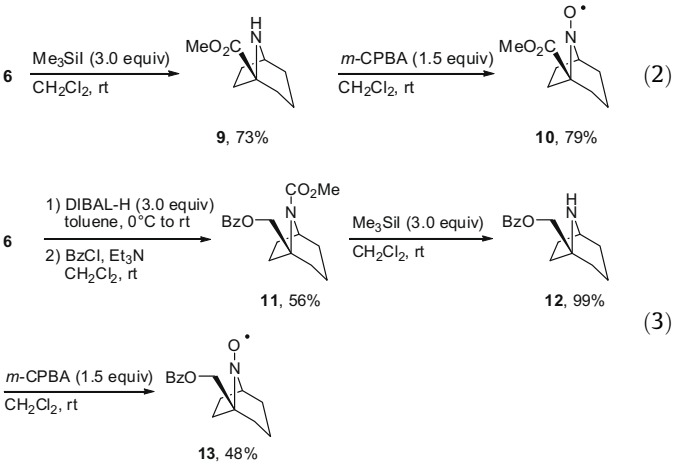
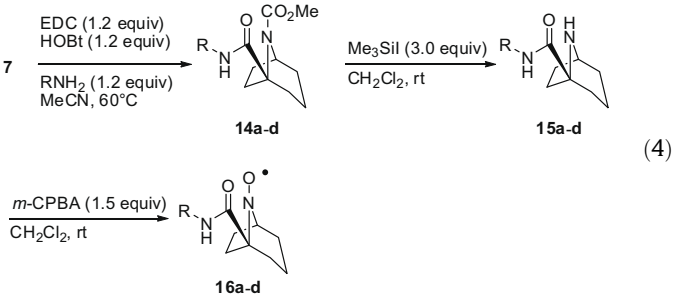
2.2. Synthesis of enantiomerically pure *N*-oxyls 10, 13, and 16a–d

Enantiomerically pure azabicyclo-*N*-oxyl **10** possessing a methoxycarbonyl group at the bridgehead position was synthesized from **6** by deprotection of the *N*-methoxycarbonyl group utilizing Me_3SiI, followed by *m*-CPBA oxidation (Eq. 2). *N*-Oxyl **13** was synthesized as follows: reduction of the methyl ester group followed by benzoylation of the hydroxyl group gave compound **11** in moderate yield. After deprotection of **11**, successive oxidation with *m*CPBA afforded *N*-oxyl **13** (Eq. 3).



Compounds **14a–d**, which were substituted with several amide groups, were prepared by using a solution-phase method (Eq. 4). *N*-Oxyls **16a–d** were prepared via a method similar to that described for the preparation of *N*-oxyl **10**. The results are summarized in Table 1.



The cyclic voltammogram for **10** showed a reversible wave pattern similar to that of TEMPO.[14] This fact strongly suggests that enantiomerically pure azabicyclo-*N*-oxyls could also play the role of an oxidation mediator such as TEMPO (Fig. 3).

2.3. Enantioselective electrooxidation of DL-1-phenylethanol mediated by chiral azabicyclo-*N*-oxyls 10, 13, and 16a–d

The enantioselective electrooxidation of DL-1-phenylethanol **17**[8a,15] mediated by chiral azabicyclo-*N*-oxyls **10**, **13**, and **16a–d** was carried out in an undivided beaker-type cell having platinum electrodes as follows (Eq. 5): that is, oxidation was conducted, using a catalytic amount of *N*-oxyl, an excess amount of sodium bromide, and a mixture of CH_2Cl_2 and saturated aqueous $NaHCO_3$ as solvent. After passing through 1.5 F/mol of electricity at constant current (20 mA, terminal voltage: ca. 3 V) at 0 °C, acetophenone **18** and (*S*)-**17** were obtained. The results are shown in Table 2. The use of *N*-oxyls **10** and **16a–d** afforded (*S*)-**17** with moderate *S* values[16] (entries 1, 3, and 4–6), while (*S*)-**17** was recovered with low enantioselectivity when *N*-oxyl **13** was used (entry 2).

The enantioselective oxidations of other *sec*-alcohols **19–24** mediated by **16b** were examined (Eq. 6). Table 3 summarizes the results. In all cases, (*S*)-alcohols **19–24** were recovered with low to moderate *S* values.

Scheme 2 shows our proposed mechanism for the kinetic resolution of DL-**17** mediated by chiral *N*-oxyl **16b**. Compound DL-**17** has prospects to approach **16b′** generated by the oxidation of **16b** with a bromonium ion from path a or path b. In the case of path a, since (*R*)-**17** can smoothly approach **16b′** to form the active intermediate, (*R*)-**17** can be easily oxidized to afford acetophenone **18**. On the other hand, the formation of intermediate composed of (*S*)-**17** and **16b** seems to be somewhat difficult. Also, in the case of path b, the intermediate seems to be somewhat unstable because the distance $O–H^a\cdots O^a{=}C$ is too long for a hydrogen bond.

3. Conclusion

We have accomplished a convenient method for synthesis of enantiomerically pure bicyclic proline analogues starting from D-pipecolinic acid. It has conformational properties similar to those of proline, which is a β-turn inducer. Chiral azabicyclo *N*-oxyls derived from bicyclic amino acid worked well as catalysts in the enantioselective electrooxidation of racemic *sec*-alcohols to afford optically active *sec*-alcohols with moderate *S* values.

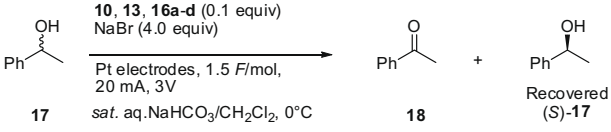
4. Experimental

4.1. General

Electrochemical reactions were carried out using DC Power Supply (GP 050–2) of Takasago Seisakusho, Inc. ^1H NMR spectra were measured on a Varian Gemini 300 and 400 spectrometer with TMS as an internal standard. ^{13}C NMR spectra were measured on a Varian Gemini 300 and 400 spectrometer with TMS as an internal standard. IR spectra were obtained on a Shimadzu FTIR-8100A. Mass spectra were obtained on a JEOL JMS-DX 303 instrument.

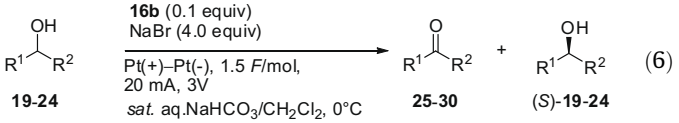
All reagents and solvents were used as supplied without further purification.

Although we could not determine the enantiomeric purities for compounds **7**, **9**, **10**, **11**, **12**, **13**, **14a–d**, **15a–d,** and **16a–d**, it was assumed that there was no racemization during their derivation from enantiomerically pure **6**.



4.2. Procedure for the synthesis of enantiomerically pure proline analogue

Methyl *N*-methoxycarbonyl-L-pipecolinate *ent*-**1**[10] and methyl *N*-methoxycarbonyl-6-methoxy-L-pipecolinate *ent*-**2**[10] are known compounds.



(6)

4.2.1. Methyl *N*-methoxycarbonyl-(6*S*)-allyl-D-pipecolinate *cis*-3

Under a nitrogen atmosphere, BF_3–OEt_2 (4.2 mL, 34.2 mmol) was added dropwise to **2** (7.5 g, 32.6 mmol) and allyltrimethylsilane (9.8 mL, 61.9 mmol) in CH_2Cl_2 (200 mL) at −78 °C, then the mixture was stirred for 3 h and allowed to stand until it warmed to −40 °C. The resulting mixture was poured into ice water and was extracted with $CHCl_3$ (300 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt = 5:1; *cis*-**3** was less polar than *trans*-**3**) to afford *cis*-**3** as a colorless oil (5.7 g, 72%). $[\alpha]_D^{20} = +106.6$ (*c* 1.0, $CHCl_3$); IR (neat) ν = 2951, 1752, 1713, 1642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 5.80–5.63 (m, 1H), 5.07–5.01 (m, 2H), 4.86 (br s, 1H), 4.21 (br s, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 2.42–2.10 (m, 3H), 1.78–1.47 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.8, 136.0, 116.8, 52.8, 52.3, 52.1, 50.8, 36.3, 26.0, 25.8, 15.3; [HR-FAB(+)]: *m*/*z* calcd for $C_{12}H_{20}NO_4$ $[M+H]^+$ 242.1393: found 242.1404.

4.2.2. Methyl *N*-methoxycarbonyl-(6*S*)-(2-hydroxyethyl)-D-pipecolinate 4

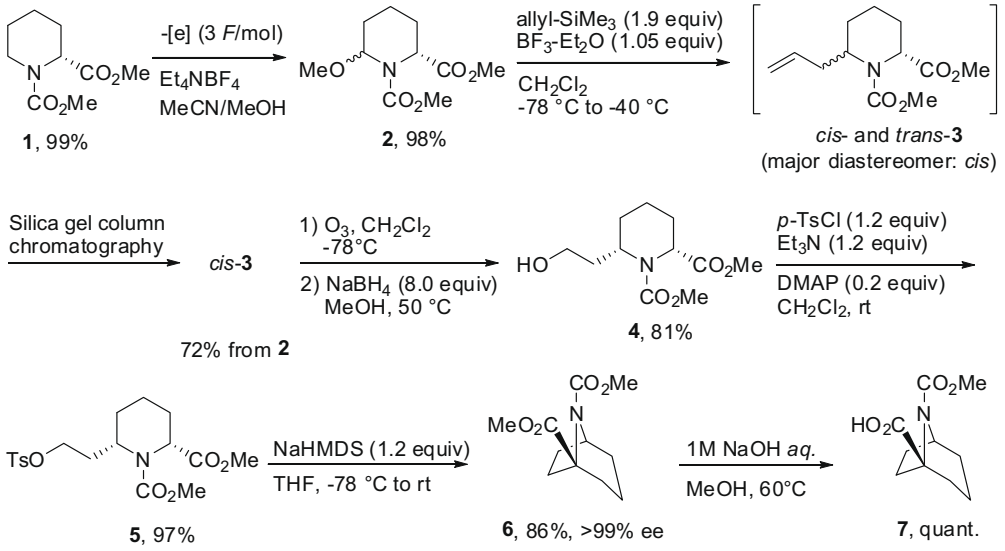
Ozone gas was bubbled into a solution of **3** (241 mg, 1.0 mmol) in CH_2Cl_2 (5.0 mL) at −78 °C, and the reaction was monitored by TLC. After the disappearance of **3**, $NaBH_4$ (304 mg, 8.0 mmol) dissolved in MeOH (1.0 mL) was added dropwise to the mixture and was stirred at 50 °C for 6 h. The mixture was poured into 3% aqueous HCl and was extracted with $CHCl_3$ (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt = 1:1) to afford **4** as a colorless oil (198 mg, 81%). $[\alpha]_D^{20} = +50.2$ (*c* 1.0, $CHCl_3$); IR (neat) ν = 3500 (br), 2953, 1736, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 4.84 (br s, 1H), 4.50 (br s, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.69–3.63 (m, 2H), 2.30 (d, *J* = 12.0 Hz, 1H), 1.81–1.43 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.8, 157.9, 58.7, 53.3, 52.4, 52.1, 46.8, 35.6, 29.4, 26.0, 16.0; [HR-FAB(+)]: *m*/*z* calcd for $C_{11}H_{20}NO_5$ $[M+H]^+$ 246.1342: found 246.1345.

4.2.3. Methyl *N*-methoxycarbonyl-(6*S*)-[2-(*p*-tolunesulfonyloxy)-ethyl]-D-pipecolinate 5

At first, *p*-TsCl (120 mg, 0.63 mmol), Et_3N (88 μL, 0.63 mmol), and 4-DMAP (13.4 mg, 0.11 mmol) were added into **4** (130 mg, 0.53 mmol) in CH_2Cl_2 (3.0 mL) and the mixture was stirred for 24 h at room temperature. Upon completion of the reaction, the mixture was poured into 3% aqueous HCl and was extracted with $CHCl_3$ (10 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt = 4:1) to afford **5** as a colorless oil (205 mg, 97%). $[\alpha]_D^{20} = +61.5$ (*c* 1.0, $CHCl_3$); IR (neat) ν = 2953, 1742, 1701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.80 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 4.89 (br s, 1H), 4.36–4.33 (m, 1H), 4.14–4.12 (m, 2H), 3.69 (s, 3H), 3.68 (s, 3H), 2.45 (s, 3H), 2.29 (d, *J* = 14.4 Hz, 1H), 2.08–1.98 (m, 1H), 1.77–1.40 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.0, 156.8, 144.6, 133.0, 129.8, 128.0, 68.4, 53.0, 52.3, 47.6, 32.0, 28.5, 25.9, 21.6, 15.7; [HR-FAB(+)]: *m*/*z* calcd for $C_{18}H_{26}NO_7S$ $[M+H]^+$ 400.1430: found 400.1449.

4.2.4. Methyl (1*R*)-*N*-methoxycarbonyl-8-azabicyclo[3.2.1] octane-1-carboxylate 6

Under a nitrogen atmosphere, 1.9 M NaHMDS (2.5 mL, 4.7 mmol) in *n*-hexane was added dropwise to **5** (1.56 g, 3.9 mmol) in THF (40 mL) at −78 °C, then the mixture was stirred at −78 °C for 12 h and allowed to stand until it warmed to room temperature. The mixture was then poured into saturated aqueous NH_4Cl and was extracted with AcOEt (40 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt = 5:1) to afford **6** as a colorless oil (761 mg, 86%). $[\alpha]_D^{23} = +25.0$ (*c* 1.0, $CHCl_3$, >99% ee); IR (neat) ν = 2953, 1750, 1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 4.33 (br s, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 2.25–1.39 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.8, 154.9, 65.2, 56.9, 52.4, 52.2, 34.1, 29.8, 29.6, 27.3, 17.0; [HR-FAB(+)]: *m*/*z* calcd for $C_{11}H_{18}NO_4$ $[M+H]^+$ 228.1236: found 228.1237. HPLC: Daicel Chiralcel OJ-H column, *n*-hexane:ethanol = 20:1, wavelength: 210 nm, flow rate: 1.0 mL/min, retention time: 8.2 min for (*S*)-**6**, 11.1 min for (*R*)-**6**.



Scheme 1.

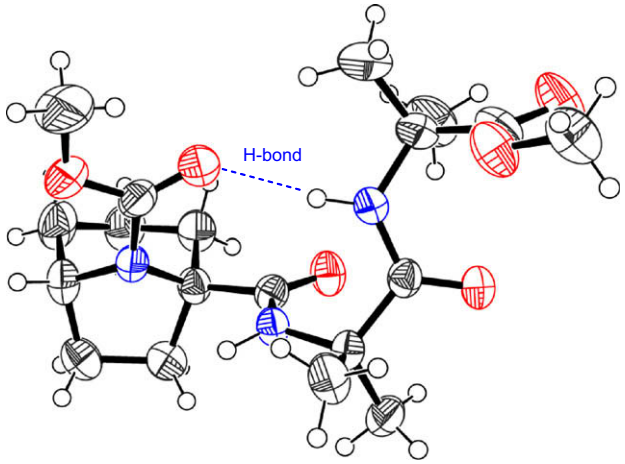
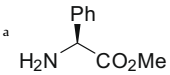
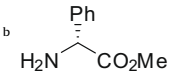


Figure 2. Ortep drawing of tripeptide **8**.

Table 1
Preparation of enantiomerically pure *N*-oxyls **16a–d**

Entry	RNH_2	Yield of **14a–d** (%)	**15a–d** (%)	**16a–d** (%)
1	Ph–NH_2	**14a** (70)	**15a** (51)	**16a** (85)
2	Bn–NH_2	**14b** (78)	**15b** (74)	**16b** (82)
3	Methyl L-Phg[a]	**14c** (78)	**15c** (86)	**16c** (86)
4	Methyl D-Ph[b]	**14d** (83)	**15d** (83)	**16d** (68)

a 

b 

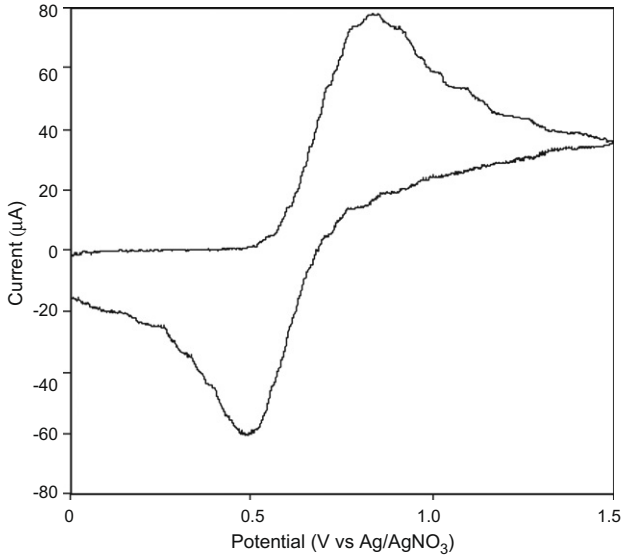
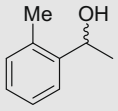
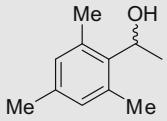
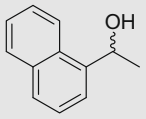
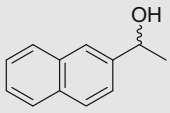
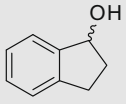
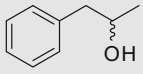


Figure 3. Cyclic voltammogram for *N*-oxyl **10**.

Table 2
Enantioselective oxidation of DL-phenylethanol (**17**) mediated by **10, 13, and 16a–d**

Entry	*N*-oxyl	Yield of **18** (%)	Yield of recovered (*S*)-**17** (%)	% ee of (*S*)-**17**	*S*
1	**10**	59	41	49	3
2	**13**	50	41	7	1
3	**16a**	64	36	53	3
4	**16b**	50	50	59	7
5	**16c**	45	51	42	4
6	**16d**	53	36	69	6

Table 3
Enantioselective oxidation of various *sec*-alcohols **19–24** mediated by **16b**

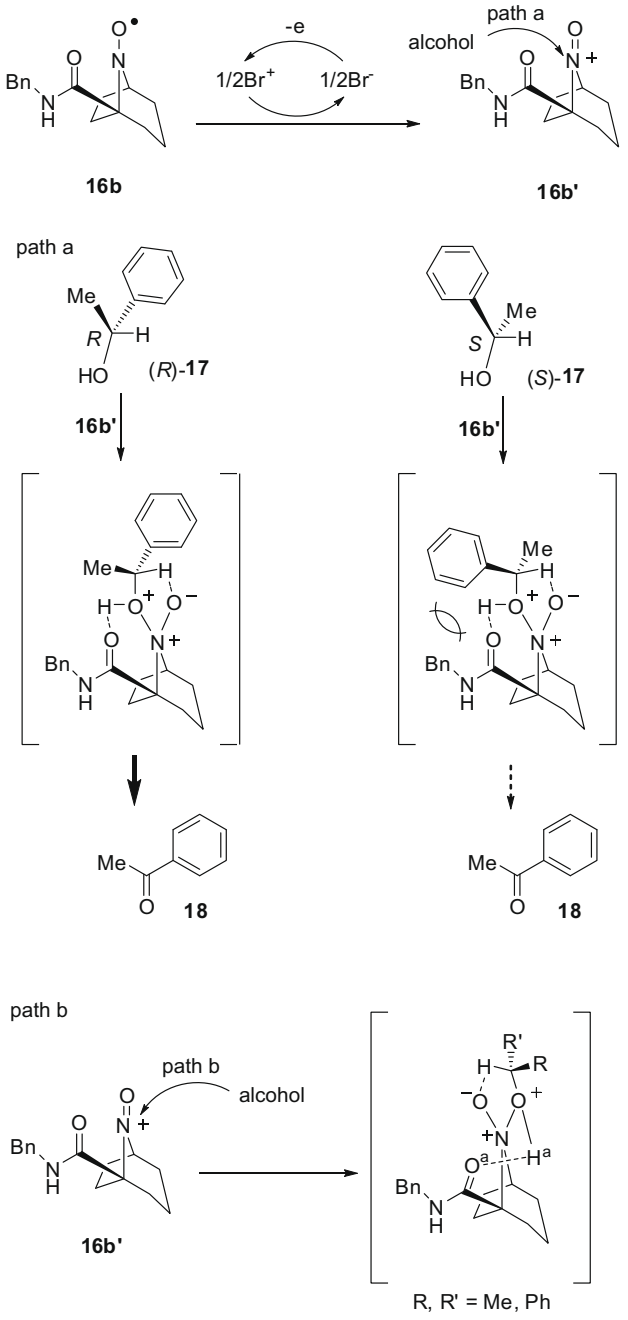
Entry	*sec*-Alcohol	Yield of ketone (%)	Yield of recovered (*S*)-alcohol	% ee of (*S*)-**19–24**	*S*
1	**19** 	**25** 50	48	33	3
2	**20** 	**26** 54	45	16	2
3	**21** 	**27** 62	35	30	2
4	**22** 	**28** 70	29	69	3
5	**23** 	**29** 53	46	38	3
5	**24** 	**30** 66	24	72	4

4.2.5. (1*R*)-*N*-Methoxycarbonyl-8-azabicyclo[3.2.1]octane-1-carboxylic acid 7

At first, 1 M aqueous NaOH (5.0 mL) was added to the stirred solution of **6** (318 mg, 1.4 mmol) in MeOH (5.0 mL), and the stirring of solution was continued at 60 °C for 48 h. The solution was then neutralized with 3% aqueous HCl, and then MeOH was evaporated. The residue was diluted with brine, extracted with AcOEt (20 mL × 3), and dried over anhydrous $MgSO_4$. Removal of the solvent afforded compound **7** (298 mg, quant.) as a colorless oil, which was used for the next reaction without further purification. $[\alpha]_D^{29} = +21.6$ (*c* 1.0, $CHCl_3$, >99% ee); IR (neat) $\nu = 3280$ (br), 2955, 1750, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 9.91$ (br s, 1H), 4.33 (br s, 1H), 3.72 (s, 3H), 2.34–1.40 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 177.3$, 155.3, 65.4, 57.2, 52.6, 34.6, 29.8, 27.3, 20.8, 17.0; [HR-FAB(+)]: *m/z* calcd for $C_{10}H_{16}NO_4$ $[M+H]^+$ 214.1079: found 214.1080.

4.2.6. Methyl *N*-[(1*R*)-*N*-methoxycarbonyl-8-azabicyclo[3.2.1]octane-1-carbonyl]dimethylglycyl-dimetylglycinate 8

A solution of **7** (213 mg, 1.0 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC, 230 mg, 1.2 mmol),



Scheme 2. Plausible stereochemical course for the kinetic resolution of DL-**17**.

and 1-hydroxybenzotriazole (HOBt, 162 mg, 1.2 mmol) in MeCN (5 mL) was stirred at room temperature for 30 min. Then, a solution of H_2N–$(Aib)_2$–OMe (202 mg, 1.0 mmol) in MeCN (5 mL) was added to the stirred solution and stirring was continued at 60 °C for 48 h. The solution was evaporated, diluted with AcOEt (50 mL), washed with 3% aqueous HCl, 5% $NaHCO_3$, and brine, and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a white solid, which was purified by column chromatography on silica gel (*n*-hexane:AcOEt = 1:5) to afford **8** (310 mg, 78%) as colorless crystals. Mp 165–167 °C; $[\alpha]_D^{25} = +25.6$ (*c* 0.5, $CHCl_3$); IR (KBr) ν = 3324, 3013, 1746, 1736, 1690, 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.79 (br s, 1H), 5.91 (br s, 1H), 4.30 (d, *J* = 6.6 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 2.21–1.42 (m, 22H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 175.3, 173.6, 159.8, 156.5, 66.8, 58.0, 56.6, 55.9, 52.8, 52.1, 35.3, 29.5, 28.4, 27.1, 25.4, 24.0, 23.6, 16.9, 14.7; [HR-FAB(+)]: *m/z* calcd for $C_{19}H_{32}N_3O_6$ $[M+H]^+$ 398.2291: found 398.2314.

Crystallographic data: orthorhombic; space group $P2_12_12_1$; *a* = 8.7962(5) Å, *b* = 10.6579(5) Å, *c* = 22.8155(11) Å; α, β, γ = 90°; *V* = 2138.93(19) $Å^3$; *Z* = 4, d_{calcd} = 1.234 g/cm^3; 15,490 reflections collected 2763 unique (R_{int} = 0.019); *R* = 0.0595, wR_2 = 0.1330.

4.3. Preparation of chiral azabicyclo *N*-oxyls

4.3.1. Methyl (1*R*)-8-azabicyclo[3.2.1]octane-1-carboxylate 9

Me_3SiI (213 μL, 1.5 mmol) was added to stirred solution of **6** (114 mg, 0.5 mmol) in CH_2Cl_2 (2.0 mL), and the solution was stirred at rt for 12 h. The solution was then poured into saturated aqueous $NaHCO_3$ and was extracted with $CHCl_3$ (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and solvent was removed under reduced pressure to afford **9** as a colorless oil, which was used for next reaction without further purification. $[\alpha]_D^{28} = +14.3$ (*c* 0.7, $CHCl_3$, >99% ee); IR (neat) ν = 3277 (br), 2953, 1717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 3.74 (s, 3H), 3.06 (br s, 2H), 2.08–1.46 (m, 10H); [HR-EI(+)]: *m/z* calcd for $C_9H_{15}NO_2$ $[M]^+$ 169.1103: found 169.1108.

4.3.2. Methyl (1*R*)-8-azabicyclo[3.2.1]octane-1-carboxylate-*N*-oxyl 10

A solution of amine **9** (34 mg, 0.2 mmol) and *m*-CPBA (52 mg, 0.3 mmol) in CH_2Cl_2 (1.0 mL) was stirred for 3 h at rt. The solution was then poured into saturated aqueous $NaHCO_3$ and was extracted with $CHCl_3$ (10 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt = 3:1) to afford *N*-oxyl **10** (29 mg, 79%) as a red foam. $[\alpha]_D^{29} = -13.9$ (*c* 0.6, $CHCl_3$, >99% ee); IR (neat) ν = 2955, 1748, 1437 cm^{-1}; [HR-FAB(+)]: *m/z* calcd for $C_9H_{14}NO_3$ $[M+H]^+$ 184.0974: found 184.0990.

4.3.3. (1*R*)-*N*-Methoxycarbonyl-1-benzoyloxymethyl-8-azabicyclo[3.2.1]octane 11

Under an argon atmosphere, 1M DIBAL-H (3.0 mL, 3.0 mmol) in *n*-hexane was added dropwise to a solution of **6** (227 mg, 1.0 mmol) in toluene (5 mL) at 0 °C. The resulting mixture was stirred for 12 h and allowed to stand until it warmed to room temperature. The solution was then poured into 3% aqueous HCl and was extracted with AcOEt (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt = 3:1) to afford (*1R*)-*N*-methoxycarbonyl-1-hydroxymethyl-8-azabicyclo[3.2.1]octane **6′** as a colorless oil (183 mg, 86%). $[\alpha]_D^{26} = -21.3$ (*c* 0.9, $CHCl_3$, >99% ee); IR (neat) ν = 3401 (br), 2946, 1673 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 5.06 (br s, 1H), 4.30 (br s, 1H), 3.77–3.59 (m, 5H), 2.15–1.25 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.2, 66.6, 66.3, 57.6, 52.2, 32.5, 31.9, 30.6, 26.0, 17.4; [HR-EI(+)]: *m/z* calcd for $C_{10}H_{17}NO_3$ $[M]^+$ 199.1208: found 199.1187.

BzCl (98 μL, 0.84 mmol) was added to a stirred solution of **6′** (149 mg, 0.7 mmol), Et_3N (147 μL, 1.05 mmol) and DMAP (43 mg, 0.35 mmol) in CH_2Cl_2 (7 mL), and the mixture was stirred at rt for 12 h. The solution was then poured into 3% aqueous HCl and was extracted with $CHCl_3$ (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt = 5:1) to afford **11** as a colorless oil (151 mg, 65%). $[\alpha]_D^{25} = +51.3$ (*c* 1.2, $CHCl_3$, >99% ee); IR (neat) ν = 2948, 1721, 1701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.02 (d, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 4.71 (s, 2H), 4.38 (br s, 1H), 3.69 (s, 3H), 2.15–1.45 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.3, 154.9, 132.9, 130.3, 129.6, 128.3, 68.9,

64.1, 57.5, 52.1, 33.0, 32.3, 30.1, 25.7, 17.6; [HR-EI(+)]: *m/z* calcd for $C_{17}H_{21}NO_4$ $[M]^+$ 303.1471: found 303.1470.

4.3.4. (1*R*)-Benzoyloxymethyl-8-azabicyclo[3.2.1]octane 12

Compound **12** was prepared in a method similar to that described for the preparation of **9** (0.5 mmol scale). 122 mg, 99% yield; colorless oil; $[\alpha]_D^{25} = +1.4$ (*c* 0.6, $CHCl_3$, >99% ee); IR (neat) ν = 3226, 2938, 1721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.05 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 4.34 (dd, *J* = 11.1, 7.8 Hz, 2H), 3.55–3.78 (m, 1H), 2.40 (br s, 1H), 1.96–1.33 (m, 10H); [HR-EI(+)]: *m/z* calcd for $C_{15}H_{19}NO_2$ $[M]^+$ 245.1416: found 245.1410.

4.3.5. (1*R*)-Benzoyloxymethyl-8-azabicyclo[3.2.1]octane-*N*-oxyl 13

Compound **13** was prepared in a method similar to that described for the preparation of **10** (0.4 mmol scale). 50 mg, 48% yield; red foam; $[\alpha]_D^{24} = +48.8$ (*c* 1.0, $CHCl_3$, >99% ee); IR (neat) ν = 2955, 1725 cm^{-1}; [HR-EI(+)]: *m/z* calcd for $C_{15}H_{18}NO_3$ $[M]^+$ 260.1287: found 260.1272.

4.3.6. (1*R*)-*N*-Methoxycarbonyl-1-*N*-phenylcarbamoyl-8-azabicyclo[3.2.1]octane 14a

A solution of aniline (109 μL, 1.2 mmol), **7** (213 mg, 1.0 mmol), EDC (230 mg, 1.2 mmol), and HOBt (162 mg, 1.2 mmol) in MeCN (10 mL) was stirred at 60 °C for 24 h, and then volatiles were evaporated. The residue was diluted with AcOEt, washed with cold 3% aqueous HCl and 5% aqueous $NaHCO_3$, and dried over anhydrous $MgSO_4$. After removal of solvent, the residue was purified by column chromatography on silica gel (*n*-hexane:AcOEt = 3:1) to give **14a** (202 mg, 70%) as colorless crystals. Mp 150–152 °C; $[\alpha]_D^{18} = +71.6$ (*c* 1.0, $CHCl_3$, >99% ee); IR (KBr) ν = 3280, 2951, 1700, 1680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.60 (br s, 1H), 7.50 (d, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 6.3 Hz, 2H), 7.08 (t, *J* = 7.0 Hz, 1H), 4.39 (br s, 1H), 3.70 (s, 3H), 2.24–1.41 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.1, 156.1, 138.0, 128.9, 123.9, 119.8, 67.0, 58.3, 52.8, 35.9, 28.7, 26.9, 16.9; [HR-FAB(+)]: *m/z* calcd for $C_{16}H_{21}N_2O_3$ $[M+H]^+$ 289.1552: found 289.1559.

4.3.7. (1*R*)-*N*-Methoxycarbonyl-1-*N*-benzylcarbamoyl-8-azabicyclo[3.2.1]octane 14b

Compound **14b** was prepared in a method similar to that described for the preparation of **14a** (1.0 mmol scale). 235 mg, 78% yield; colorless crystals; Mp 126–128 °C; $[\alpha]_D^{25} = +70.8$ (*c* 1.0, $CHCl_3$, >99% ee); IR (KBr) ν = 3280, 2950, 1701, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.31–7.22 (m, 5H), 6.14 (br s, 1H), 4.45 (br s, 2H), 4.29 (br s, 1H), 3.60 (s, 3H), 2.12–1.36 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.0, 155.9, 138.5, 129.4, 128.5, 128.0, 127.3, 100.5, 66.4, 58.2, 52.4, 43.5, 36.3, 28.9, 26.8, 17.0; [HR-FAB(+)]: *m/z* calcd for $C_{17}H_{23}N_2O_3$ $[M+H]^+$ 303.1708: found 303.1712.

4.3.8. Methyl *N*-[(1*R*)-*N*-methoxycarbonyl-8-azabicyclo[3.2.1]octane-1-carbonyl]-L-phenylglycinate 14c

Compound **14c** was prepared in a method similar to that described for the preparation of **14a** (1.6 mmol scale). 449 mg, 78% yield; colorless oil; $[\alpha]_D^{25} = +53.0$ (*c* 0.9, $CHCl_3$, >99% ee); IR (neat) ν = 2953, 1744, 1702, 1682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.38–7.28 (m, 5H), 6.94 (br s, 0.6H), 6.65 (d, *J* = 7.5 Hz, 0.4H), 5.59 (t, *J* = 7.0 Hz, 1H), 4.34 (br s, 1H), 3.74–3.36 (m, 6H), 2.34–1.58 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.5, 171.3, 155.9, 128.9, 128.8, 128.3, 127.5, 127.1, 66.3, 58.3, 58.2, 56.1, 52.7, 52.3, 36.1, 28.8, 26.8, 17.0; [HR-EI(+)]: *m/z* calcd for $C_{19}H_{24}N_2O_5$ $[M]^+$ 360.1685: found 360.1693.

4.3.9. Methyl *N*-[(1*R*)-*N*-methoxycarbonyl-8-azabicyclo[3.2.1]octane-1-carbonyl]-D-phenylglycinate 14d

Compound **14d** was prepared in a method similar to that described for the preparation of **14a** (1.6 mmol scale). 478 mg, 83% yield; colorless oil; $[\alpha]_D^{25} = +74.7$ (*c* 0.9, $CHCl_3$, >99% ee); IR (neat) ν = 3300, 2954, 1717, 1699, 1684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.39–7.28 (m, 5H), 6.94 (br s, 0.4H), 6.65 (d, *J* = 6.9 Hz, 0.6H), 5.59 (t, *J* = 7.0 Hz, 1H), 4.34 (br s, 1H), 3.73–3.35 (m, 6H), 2.35–1.59 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.5, 171.5, 155.9, 128.9, 128.8, 128.5, 127.5, 127.1, 66.2, 58.4, 58.1, 56.1, 52.6, 52.3, 36.3, 28.8, 26.8, 16.9; [HR-EI(+)]: *m/z* calcd for $C_{19}H_{24}N_2O_5$ $[M]^+$ 360.1685: found 360.1677.

4.3.10. (1*R*)-*N*-Phenylcarbamoyl-8-azabicyclo[3.2.1]octane 15a

Compound **15a** was prepared in a method similar to that described for the preparation of **9** (0.5 mmol scale). 59 mg, 51% yield; colorless oil; $[\alpha]_D^{27} = +74.6$ (*c* 0.6, $CHCl_3$, >99% ee); IR (neat) ν = 3314, 3278, 2928, 1665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.01 (br s, 1H), 7.58 (d, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 6.9 Hz, 2H), 7.07 (t, *J* = 7.0 Hz, 1H), 3.67–3.65 (m, 1H), 2.31–1.40 (m, 11H); [HR-FAB(+)]: *m/z* calcd for $C_{14}H_{19}N_2O$ $[M+H]^+$ 231.1498: found 231.1497.

4.3.11. (1*R*)-*N*-Benzylcarbamoyl-8-azabicyclo[3.2.1]octane 15b

Compound **15b** was prepared in a method similar to that described for the preparation of **9** (0.8 mmol scale). 144 mg, 74% yield; colorless oil; $[\alpha]_D^{28} = +28.2$ (*c* 0.6, $CHCl_3$, >99% ee); IR (neat) ν = 3320, 3252, 2928, 1715, 1659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.33–7.20 (m, 6H), 4.43 (d, *J* = 9.0 Hz, 2H), 3.57–3.55 (m, 1H), 2.27–1.40 (m, 11H); [HR-FAB(+)]: *m/z* calcd for $C_{15}H_{21}N_2O$ $[M+H]^+$ 245.1654: found 245.1647.

4.3.12. Methyl *N*-[(1*R*)-8-azabicyclo[3.2.1]octane-1-carbonyl]-L-phenylglycinate 15c

Compound **15c** was prepared in a method similar to that described for the preparation of **9** (1.2 mmol scale). 340 mg, 86% yield; colorless oil; $[\alpha]_D^{24} = +0.8$ (*c* 0.6, $CHCl_3$, >99% ee); IR (neat) ν = 3366, 3277, 2930, 1748, 1676 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.93 (d, *J* = 7.2 Hz, 0.5H), 7.83 (d, *J* = 7.2 Hz, 0.5H), 7.37–7.25 (m, 5H), 5.53 (t, *J* = 6.9 Hz, 1H), 3.72 (s, 3H), 3.69–3.57 (m, 1H), 2.25–1.32 (m, 11H); [HR-EI(+)]: *m/z* calcd for $C_{17}H_{22}N_2O_3$ $[M]^+$ 302.1630: found 302.1614.

4.3.13. Methyl *N*-[(1R)-8-azabicyclo[3.2.1]octane-1-carbonyl]-D-phenylglycinate 15d

Compound **15d** was prepared in a method similar to that described for the preparation of **9** (1.3 mmol scale). 328 mg, 83% yield; Colorless oil; $[\alpha]_D^{20} = +1.4$ (*c* 0.6, $CHCl_3$, >99% ee); IR (neat) ν = 3226 (br), 2938, 1721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.86 (d, *J* = 7.2 Hz, 0.4H), 7.77 (d, *J* = 7.2 Hz, 0.6H), 7.32–7.22 (m, 5H), 5.46 (t, *J* = 7.0 Hz, 1H), 3.64 (s, 3H), 3.55–3.41 (m, 1H), 2.09–1.26 (m, 11H); [HR-EI(+)]: *m/z* calcd for $C_{17}H_{22}N_2O_3$ $[M]^+$ 302.1630: found 302.1628.

4.3.14. (1*R*)-*N*-Phenylcarbamoyl-8-azabicyclo[3.2.1]octane-*N*-oxyl 16a

Compound **16a** was prepared in a method similar to that described for the preparation of **10** (0.2 mmol scale). 42 mg, 85% yield; red foam; $[\alpha]_D^{29} = +72.1$ (*c* 0.9, $CHCl_3$, >99% ee); IR (neat) ν = 3256, 2953, 1686, 1447 cm^{-1}; [HR-FAB(+)]: *m/z* calcd for $C_{14}H_{18}N_2O_2$ $[M+H]^+$ 246.1369: found 246.1366.

4.3.15. (1*R*)-*N*-Benzylcarbamoyl-8-azabicyclo[3.2.1]octane-*N*-oxyl 16b

Compound **16b** was prepared in a method similar to that described for the preparation of **10** (0.6 mmol scale). 127 mg, 82%

yield; red foam; $[\alpha]_D^{29} = +18.7$ (*c* 0.6, $CHCl_3$, >99% ee); IR (neat) $\nu = 3270, 2951, 1721, 1650, 1478\ cm^{-1}$; [HR-FAB(+)]: *m/z* calcd for $C_{15}H_{20}N_2O_2$ $[M+H]^+$ 260.1525: found 260.1500.

4.3.16. Methyl *N*-[(1*R*)-8-azabicyclo[3.2.1]octane-1-carbonyl]-L-phenylglycinate-*N*-oxyl 16c

Compound **16c** was prepared in a method similar to that described for the preparation of **10** (1.1 mmol scale). 300 mg, 86% yield; red oil; $[\alpha]_D^{25} = +86.1$ (*c* 0.8, $CHCl_3$, >99% ee); IR (neat) $\nu = 3283, 2953, 1745, 1674\ cm^{-1}$; [HR-EI(+)]: *m/z* calcd for $C_{17}H_{21}N_2O_4$ $[M]^+$ 317.1501: found 317.1511.

4.3.17. Methyl *N*-[(1*R*)-8-azabicyclo[3.2.1]octane-1-carbonyl]-D-phenylglycinate-*N*-oxyl 16d

Compound **16d** was prepared in a method similar to that described for the preparation of **10** (1.0 mmol scale). 216 mg, 68% yield; red oil; $[\alpha]_D^{25} = +119.7$ (*c* 1.3, $CHCl_3$, >99% ee); IR (neat) $\nu = 3277, 2955, 1746, 1676\ cm^{-1}$; [HR-EI(+)]: *m/z* calcd for $C_{17}H_{21}N_2O_4$ $[M]^+$ 317.1501: found 317.1488.

4.4. General procedure for the enantioselective electrooxidation of DL-*sec*-alcohols 17, 19–24 with *N*-oxyls 10, 13, and 16a–d

Anodic oxidation of DL-1-phenylethanol DL-**17** was carried out using platinum electrodes (1 cm × 2 cm) in an undivided beaker-type cell. DL-**17** (61 mg, 0.5 mmol), **10** (9.2 mg, 0.05 mmol), and NaBr (206 mg, 2.0 mmol) were then added into a mixture of CH_2Cl_2 (2.5 mL) and saturated aqueous $NaHCO_3$ (2.5 mL). After passing through 1.5 F/mol of electricity at a constant current (20 mA) at 0 °C, the mixture was poured into water and was extracted with AcOEt (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt = 10:1) to afford acetophenone **18** (35.4 mg, 59% yield) and (*S*)-**17** (24.6 mg, 41% yield) as a colorless oil.

The enantiomeric purity of (*S*)-**17** was determined by chiral HPLC: Daicel Chiralcel OB column (4.6 mmφ, 250 mm), *n*-hexane:2-propanol = 15:1, wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 13.5 min for (*S*)-**17**, 17.5 min for (*R*)-**17**.

The enantiomeric purity of (*S*)-**19** was determined by chiral HPLC: Daicel Chiralcel OB column (4.6 mmϕ, 250 mm), *n*-hexane:2-propanol = 15:1, wavelength: 254 nmϕ, flow rate: 0.5 mL/min, retention time: 11.9 min for (*S*)-**19**, 16.9 min for (*R*)-**19**.

The enantiomeric purity of (*S*)-**20** was determined by chiral HPLC: Daicel Chiralcel AD column (4.6 mmϕ, 250 mm), *n*-hexane:2-propanol = 100:1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 14.0 min for (*R*)-**20**, 16.5 min for (*S*)-**20**.

The enantiomeric purity of (*S*)-**21** was determined by chiral HPLC: Daicel Chiralcel OJ column (4.6 mmϕ, 250 mm), *n*-hexane:2-propanol = 9:1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 13.8 min for (*S*)-**21**, 16.8 min for (*R*)-**21**.

The enantiomeric purity of (*S*)-**22** was determined by chiral HPLC: Daicel Chiralcel OJ column (4.6 mmϕ, 250 mm), *n*-hexane:2-propanol = 9:1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 12.7 min for (*S*)-**22**, 16.0 min for (*R*)-**22**.

The enantiomeric purity of (*S*)-**23** was determined by chiral HPLC: Daicel Chiralcel OB column (4.6 mmϕ, 250 mm), *n*-hexane:2-propanol = 15:1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 15.0 min for (*R*)-**23**, 27.0 min for (*S*)-**23**.

The enantiomeric purity of (*S*)-**24** was determined by chiral HPLC: Daicel Chiralcel OD-H column (4.6 mmϕ, 250 mm), *n*-hexane:2-propanol = 50:1, wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 21.0 min for (*S*)-**24**, 22.5 min for (*R*)-**24**.

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References

1. (a) Maity, P.; König, B. *Biopolymers (Pept. Sci.)* **2008**, *90*, 8–27; (b) Tanaka, M. *Chem. Pham. Bull.* **2007**, *55*, 349–358.
2. (a) Cabrera, S.; Reyes, E.; Alemán, J.; Milelli, A.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 12031–12037; (b) Tayama, E.; Kimura, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 8869–8871; (c) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569–623; (d) Kawabata, T.; Matsuda, S.; Kawakami, S.; Monguchi, D.; Moriyama, K. *J. Am. Chem. Soc.* **2006**, *128*, 15394–15395; (e) Ooi, T.; Takeuchi, M.; Kato, D.; Uematsu, Y.; Tayama, E.; Sakai, D.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 5073–5083.
3. (a) Alonso de Diego, S. A.; Gutierrez-Rodríguez, M.; Pérez de Vega, M. J.; Casabona, D.; Cativiela, C.; González-Muñiz, R.; Herranz, R.; Cenarruzabeitia, E.; Frechilla, D.; Del Río, J.; Jimeno, M. L.; García-López, M. T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1392–1396; (b) Han, W.; Pelletier, J. C.; Mersinger, L. J.; Kettner, C. A.; Hodge, C. N. *Org. Lett.* **1999**, *1*, 1875–1877.
4. (a) Alemán, C.; Jiménez, A. I.; Cativiela, C.; Pérez, J. J.; Casanovas, J. *J. Phys. Chem. B* **2005**, *109*, 11836–11841; (b) Gil, A. M.; Buñuel, E.; Jiménez, A. I.; Cativiela, C. *Tetrahedron Lett.* **2003**, *44*, 5999–6002; (c) Avenoza, A.; Busto, J. H.; Peregrina, J. M.; Rodríguez, F. *J. Org. Chem.* **2002**, *67*, 4241–4249.
5. (a) Gil, A. M.; Orús, E.; López-Carrillo, V.; Buñuel, E.; Cativiela, C. *Tetrahedron: Asymmetry* **2005**, *16*, 3115–3123; (b) Gil, A. M.; Buñuel, E.; López, P.; Cativiela, C. *Tetrahedron: Asymmetry* **2004**, *15*, 811–819; (c) Gil, A. M.; Buñuel, E.; Díaz-de-Villegas, M. D.; Cativiela, C. *Tetrahedron: Asymmetry* **2003**, *14*, 1479–1488; (d) Campbell, J. A.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 6313–6325.
6. For β-amino acids: Otani, Y.; Futaki, S.; Kiwada, T.; Sugiura, Y.; Muranaka, A.; Kobayashi, N.; Uchiyama, M.; Yamaguchi, K.; Ohwada, T. *Tetrahedron* **2006**, *62*, 11635–11644.
7. The synthesis of *racemic* proline analogue **A1** has been recently reported: Casabona, D.; Jiménez, A. I.; Cativiela, C. *Tetrahedron* **2007**, *63*, 5056–5061.
8. (a) Shiigi, H.; Mori, H.; Tanaka, T.; Demizu, Y.; Onomura, O. *Tetrahedron Lett.* **2008**, *49*, 5247–5251; (b) Demizu, Y.; Shiigi, H.; Oda, T.; Matsumura, Y.; Onomura, O. *Tetrahedron Lett.* **2008**, *49*, 48–52.
9. (a) Libendi, S. S.; Demizu, Y.; Matsumura, Y.; Onomura, O. *Tetrahedron* **2008**, *64*, 3935–3942; (b) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264–4268.
10. Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1986**, *51*, 2590–2592.
11. Intermolecular alkylations: (a) Matsumura, Y.; Inoue, M.; Nakamura, Y.; Talib, I. L.; Maki, T.; Onomura, O. *Tetrahedron Lett.* **2000**, *41*, 4619–4622; (b) Matsumura, Y.; Kinoshita, T.; Yanagihara, Y.; Kanemoto, N.; Watanabe, M. *Tetrahedron Lett.* **1996**, *37*, 8395–8398.
12. Crystallographic data for structure of tripeptide **8** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 699629. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK; fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.
13. Ravi, A.; Balaram, P. *Tetrahedron* **1984**, *40*, 2577–2583.
14. Cyclic voltammogram for **10** was measured in 0.1 M Et_4NBF_4/MeCN solution using glassy-carbon as a working electrode, platinum as a counter electrode, and Ag/0.01 M $AgNO_3$ as a reference electrode. Concentration of **10**: 1.0 mM. Scan rate: 30 mV/s. Cyclic voltammogram for other *N*-oxyls showed reversible wave pattern similar to that for **10**. Oxidation potential: 0.83 V for **10**, 0.82 V for **13**, 0.58 V for **16a**, 0.79 V for **16b**, 0.78 V for **16c**, 0.80 V for **16d**.
15. (a) Ma, Z.; Huang, Q.; Bobbit, J. M. *J. Org. Chem.* **1993**, *58*, 4837–4843; (b) Rychnovsky, S. D.; McLernon, T. L.; Rajapakse, H. *J. Org. Chem.* **1996**, *61*, 1194–1195; (c) Kashiwagi, Y.; Kurashima, F.; Kikuchi, C.; Anzai, J.; Osa, T.; Bobbit, J. M. *Tetrahedron Lett.* **1999**, *40*, 6469–6472; (d) Kuroboshi, M.; Yoshihisa, H.; Cortona, M. N.; Kawakami, Y.; Gao, Z.; Tanaka, H. *Tetrahedron Lett.* **2000**, *41*, 8131–8135.
16. Kagan, H. B.; Fiaud, J. C.. In *Topics in Stereochemistry*; Eliel, E. L., Ed.; Wiley & Sons: New York, 1988; Vol. 18, pp 249–330.