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Preparation and Characterization of New Chiral Nitronyl Nitroxides Bearing a Stereogenic Center in the Imidazolyl Framework

Satoshi Shimono, Rui Tamura,* Naohiko Ikuma, Tatsuya Takimoto, Naoyuki Kawame, Osamu Tamada, Naoko Sakai, Hiroaki Matsuura, and Jun Yamauchi

Graduate School of Human and Environmental Studies, Kyoto University, Kyoto 606-8501, Japan

tamura@fischer.jinkan.kyoto-u.ac.jp

Received October 2, 2003

A synthetic procedure for optically active and racemic α-nitronyl nitroxides (α-NNs) having a stereogenic center at the 4-position of the imidazolyl ring is described. This procedure consists of (1) the synthesis of a dissymmetric *vic*-dinitro compound by Kornblum reaction, (2) the enantiomeric resolution of the racemate by a diastereomer method for obtaining the optically active sample, (3) the quick reduction of the optically active or racemic *vic*-dinitro compound to the bis(hydroxyamino) derivative with Al/Hg, (4) the solvent-free condensation of the bis(hydroxyamino) compound with an aldehyde to give the 1,3-dihydroxyimidazolidine, and (5) the final oxidation of the α-NN precursor with aqueous $NaIO_4$. The absolute configuration of the optically active α-NNs was assigned by correlating with the X-ray crystal structure of the (−)-(1*S*,4*R*)-camphanic acid ester derivative of the optically active *vic*-dinitro compound. The molecular conformation of the optically active α-NNs was found to be folded both in solution and in the solid state by CD spectroscopy and energy minimization with the Monte Carlo method. The magnetic properties of both optically active and racemic α-NNs in solution and in the solid state were characterized by EPR spectroscopy and magnetic susceptibility measurement, respectively.

Introduction

Since ferromagnetic transition and ordering at low temperatures was first observed by Kinoshita et al. with respect to the achiral crystalline phase of a purely organic, achiral α-nitronyl nitroxide (α-NN), which satisfies the magnetic requirements in the solid state such as favored intra- and intermolecular spin-polarization exchange coupling and an avoidance of intermolecular SOMO-SOMO overlapping,[1] a large number of achiral α-NN derivatives have been prepared to obtain the second and the third examples. To date more than 10 organic ferromagnets have been found with respect to the chiral or the achiral crystalline phase of purely organic, achiral nitroxide radicals including α-NNs and other types.[2,3] Furthermore, since a theoretically predicted magnetochiral dichroism (MChD), which arises from an intramolecular interaction between the magnetic and electric dipole transition moments in the excited state, was experimentally proved in solution for optically active europium(III) complexes in the applied magnetic field,[4] several optically active nitroxide radicals and their metal complexes have been prepared with the aim of observing a strong magnetochiral effect for chiral molecular magnets.[5]

Although a number of simple chiral nitroxide radicals bearing a stereogenic center at the quarternary carbon atom adjacent to the NO radical moiety have successfully been synthesized and utilized as spin probes or spin labeling agents, and organic chiral mediators for kinetic oxidation,[6,7] there have been only two reports concerning the chiral α-NN version; in both cases only racemates were obtained.[8,9] The actual synthesis of optically active

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10.1021/jo0354443 CCC: $27.50
Published on Web 12/19/2003

α-NNs thus far obtained has been limited to the simple incorporation of an enantiomerically enriched substituent on the 2-position of the imidazolyl ring.[5]

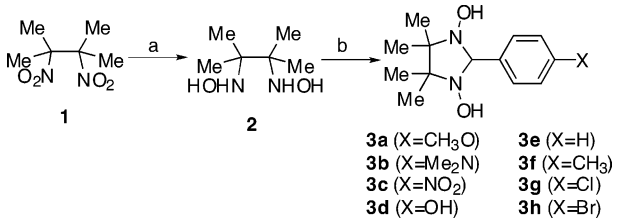
We report here (1) the optimization of the reaction conditions for the synthesis of chiral α-NNs having a stereogenic center at the 4-position of the imidazolyl ring and (2) the first preparation of this type of optically active α-NNs, through (i) the synthesis of a dissymmetric *vic*-dinitro compound by the Kornblum reaction,[10] (ii) the subsequent enantiomeric resolution of the racemate by a diastereomer method for the optically active sample, (iii) the conversion of the *vic*-dinitro compound to the corresponding bis(hydroxyamino) compound by reduction with Al/Hg with high reproducibility,[9,11] (iv) the efficient solvent-free condensation of the bis(hydroxyamino) compound with an aldehyde in the presence of *p*-TsOH catalyst giving the corresponding dihydroxyimidazolidine, and (v) the final oxidation by $NaIO_4$ giving the optically active and racemic α-NN. Furthermore, the absolute configuration of the optically active α-NN obtained has been assigned by correlating with the X-ray crystal structure of the (−)-(1*S*,4*R*)-camphanic acid ester derivative of the optically active *vic*-dinitro compound, their molecular folding conformation has been proved by CD spectroscopy and energy minimization with the Monte Carlo method, and their magnetic properties in solution and in the solid state have been characterized by EPR spectroscopy and magnetic susceptibility measurement, respectively. The strategy described here would provide a general route to an optically active α-NN with a functionalized and dissymmetric imidazolyl framework.

Results and Discussion

Improved Synthetic Procedure for Achiral 1,3-Dihydroxyimidazolidines from Symmetric *vic*-Dinitro Compounds. Recently it has been pointed out that the well-known synthetic procedure by Ullman for the bis(hydroxyamino) compound by reduction of the precursor *vic*-dinitro compound with zinc in an ammonium chloride (Zn/NH_4Cl) buffered solution is less reliable.[8,9,12] In fact, when this conventional procedure was applied to the synthesis of chiral α-NNs from dissymmetric *vic*-dinitro comopunds, in most cases the results were indeed miserable. This is because the resulting dissymmetric bis(hydroxyamino) compounds are unstable in solution and susceptible to gradual decomposition upon prolonged reaction time. Therefore, quick reduction of a dinitro compound to the bis(hydroxyamino) derivative and its subsequent solvent-free condensation with an aldehyde seems necessary to overcome this intractable problem.

To inspect this consideration, first we have searched an appropriate reducing agent for the quick conversion of the dinitro compound **1** to the bis(hydroxyamino) compound **2** (Scheme 1). Consequently, it has been found that the use of aluminum amalgam (Al/Hg) (Al/Al^{3+}: $E° = -1.66$ V) in aqueous THF (v/v 1:20) at 0 °C for a short time (20 min) gives a better result (76% yield) reproducibly than that (less than 60% yield) of the Zn/NH_4Cl system (Zn/Zn^{2+}: $E° = -0.763$ V), as pointed out by Harada et al. (Scheme 1).[9,11]

SCHEME 1[a]



[a] Reagents and conditions: (a) Al/Hg, aq THF, 0 °C, 76%; (b) 4-X-C_6H_4CHO, 5 mol % TsOH, solvent-free, rt.

TABLE 1. Solvent-Free Synthesis of Achiral 1,3-Dihydroxyimidazolidines 3 (Scheme 1)[a]

entry	aldehyde	conditions[b]	product	isolated yield (%)
1	4-MeO-C_6H_4CHO	a	**3a**	22 (14)[c] (9)[d]
2		b	**3a**	65
3		c	**3a**	72
4	4-Me_2N-C_6H_4CHO	a	**3b**	17
5		c	**3b**	73
6	4-O_2N-C_6H_4CHO	a	**3c**	34
7		c	**3c**	62
8	4-HO-C_6H_4CHO	a	**3d**	47
9		c	**3d**	65
10	C_6H_5CHO	a	**3e**	74
11		c	**3e**	82
12	4-Me-C_6H_4CHO	a	**3f**	75
13		c	**3f**	81
14	4-Cl-C_6H_4CHO	a	**3g**	76
15		c	**3g**	70
16	4-Br-C_6H_4CHO	a	**3h**	80
17		c	**3h**	68

[a] A mixture of bis(hydroxyamine) **2** and aldehyde are reacted at 25 °C for 48 h. [b] (a) Reaction run in MeOH. (b) Solvent-free reaction. (c) Solvent-free reaction in the presence of 5 mol % of *p*-TsOH. [c] Reaction run in EtOH. [d] Reaction run in the mixed solvent of EtOH and PhH (v/v 1:1).

The next step is to investigate the possibility of the solvent-free condensation of **2** with various aldehydes. When a mixture of **2** and *p*-anisaldehyde was stirred in MeOH for 48 h at 25 °C according to Ullman's procedure,[12] the isolated yield of the product **3a** was only 22% (entry 1 in Table 1). Neither longer nor shorter reaction time improved the yield and the use of other solvents led to comparable or worse results (entry 1). In contrast, when an equimolar mixture of solid **2** and *p*-anisaldehyde was mixed in a flask with a stirbar for 48 h at 25 °C without solvents, followed by washing the solid reaction mixture with H_2O and EtOH, pure **3a** was obtained in 65% yield (entry 2). Addition of 5 mol % of *p*-TsOH to the solvent-free reaction further improved the yield to 72% (entry 3). Likewise, the solvent-free reaction of **2** with other aldehydes in the presence of 5 mol % of *p*-TsOH led to better results for the products **3b**, **3c**, **3d**, **3e**, and **3f** than the use of MeOH as the solvent (entries 4−13), while comparable or slightly less yields were obtained for **3g** and **3h** (entries 14−17).

Preparation of Chiral Racemic α-NNs and Their Magnetic Properties. With these improved results in hand, we have examined the synthesis of chiral 1,3-dihydroxyimidazolidines from dissymmetric *vic*-dinitro compounds (Scheme 2). For the synthesis of the chiral

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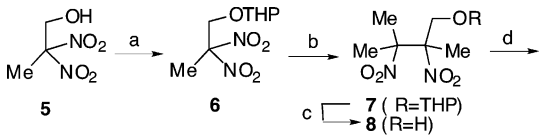
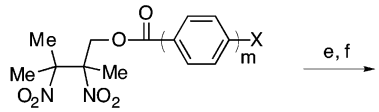
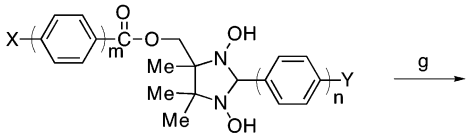
SCHEME 2[a]

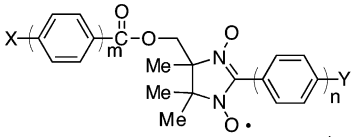




(±)-**9**: m=1, X=OMe (98%)
(R)-**9**: m=1, X=OMe (96%)
(±)-**10a**: m=1, X=OC_8H_{17} (72%)
(±)-**10b**: m=2, X=OC_8H_{17} (60%)
(R)-**10b**: m=2, X=OC_8H_{17} (56%)
(±)-**10c**: m=1, X=$OC_{12}H_{25}$ (73%)
(±)-**10d**: m=2, X=$OC_{12}H_{25}$ (58%)



(±)-**11**: m=n=1, X=OMe, Y=H (50%)[b]
(±)-**12**: m=n=1, X=OMe, Y=Br (54%)[b]
(R)-**12**: m=n=1, X=OMe, Y=Br (52%)[b]
(R)-**13b**: m=n=2, X=Y=OC_8H_{17} (33%)[c]



(±)-**14**: m=n=1, X=OMe, Y=H (54%)[d]
(±)-**15**: m=n=1, X=OMe, Y=Br (60%)[e]
(R)-**15**: m=n=1, X=OMe, Y=Br (57%)[e]
(±)-**16a**: m=1, n=2, X=Y=OC_8H_{17} (21%)[f]
(±)-**16b**: m=n=2, X=Y=OC_8H_{17} (19%)[f]
(R)-**16b**: m=n=2, X=Y=OC_8H_{17} (13%)[f]
(±)-**16c**: m=n=1, X=Y=$OC_{12}H_{25}$ (17%)[f]
(±)-**16d**: m=2, n=1, X=Y=$OC_{12}H_{25}$ (10%)[f]
(±)-**16e**: m=n=2, X=Y=$OC_{12}H_{25}$ (10%)[f]

[a] Reagents and conditions: (a) DHP, PPTS, DCM, rt, 79%; (b) Me_2CNO_2Li, DMSO, rt, 90%; (c) I_2, MeOH, 50 °C, 91%; (d) $X(C_6H_4)_mCOCl$, Et_3N, DMAP, DCM, rt; (e) Al/Hg, THF, 0 °C; (f) $Y(C_6H_4)_nCHO$, 5 mol % TsOH, rt; (g) $NaIO_4$, $H_2O/CHCl_3$, rt. [b]Crude yield from **9**. [c]Crude yield from (*R*)-**10b**. [d]Isolated yield from **11**. [e]Isolated yield from **12**. [f]Overall isolated yield from **10**.

racemic *vic*-dinitro alcohol **8**, the *gem*-dinitro compound **6** derived from known **5**[13] was reacted with the lithium salt of 2-nitropropane in DMSO at 25 °C to give (±)-**7** in 90% yield.[10] Compound (±)-**9** obtained by 4-methoxybenzoylation of (±)-**8** was subjected to reduction with Al/Hg to give the crude bis(hydroxyamino) compound, which was immediately used for the solvent-free condensation with benzaldehyde or *p*-bromobenzaldehyde to afford crude 1,3-dihydroxyimidazolidine (±)-**11** or (±)-**12** in 50% or 54% overall yield from (±)-**9**, respectively. For comparison, when the crude bis(hydroxyamino) compound obtained by Al/Hg reduction of (±)-**9** was reacted with benzaldehyde in MeOH at 25 °C for 48 h, the overall yield of crude (±)-**11** from (±)-**9** was only 10%.

As the oxidizing agent for the conversion of chiral 1,3-dihydroxyimidazolidines to the α-NNs, aqueous $NaIO_4$ was the best choice to give the corresponding α-NNs with high reproducibility; the chiral α-NNs (±)-**14** and (±)-**15** were obtained in 54% and 60% yield from (±)-**11** and (±)-**12**, respectively (Scheme 2).

To ascertain the generality of this modified synthetic method for chiral α-NNs and to investigate the possibility of applying this method to the preparation of the mesogenic materials containing a chiral nitroxide radical moiety as a paramagnetic center in the core portion, we have synthesized the model compounds (±)-**16a**−**e**. The chiral *vic*-dinitro compounds (±)-**10a**−**d** were prepared by acylation of (±)-**8** and were successively subjected to reduction with Al/Hg, solvent-free condensation with an aldehyde in the presence of *p*-TsOH catalyst, and oxidation with aqueous $NaIO_4$ without purification of each product, affording the desired α-NNs (±)-**16a**−**e** in 10−21% overall isolated yields from the corresponding (±)-**10** with full reproducibility (Scheme 2). These yields are comparable to those of (±)-**14** and (±)-**15**.

The magnetic and thermal properties of the obtained racemic chiral α-NNs are summarized in Table 2. Solutions of the α-NNs in THF display characteristic equally spaced five lines with relative intensities of 1:2:3:2:1 in their EPR spectra at 25 °C in all cases. Measurement of the molar magnetic susceptibility χ_{mol} of the polycrystalline or liquid sample of each radical compound at temperatures ranging between 2 and 300 K, using SQUID magnetometer, indicates that all the racemic samples show weak antiferromagnetic interactions in the solid state for (±)-**16a**−**e** and in the condensed phase for (±)-**15** without noticeable magnetic phase transition over this temperature range.

Preparation and Characterization of Optically Active α-NNs. To obtain optically active α-NNs, we tried an enantiomeric resolution of the *vic*-dinitro alcohol (±)-**8**, which was found to exist as a racemic compound in the crystalline state by X-ray crystallographic analysis, by means of (1) the complexation with various chiral host compounds derived from enantiopure tartaric acid[14] or (2) the acetylation with vinyl acetate, using lipases such as PS, AK, LPL, and so on.[15] However, these attempts were totally unsuccessful due to the peculiar molecular structure of **8**. Then we searched an appropriate resolving agent for the formation of the separable diastereomers. Consequently, the diastereomeric esters **17a** and **17b** formed between (−)-(1*S*,4*R*)-camphanic acid and (±)-**8** were found to be separable from each other by flash column chromatography on silica gel (hexane/EtOAc 9:1)[16] (Scheme 3). The diastereomer **17a** eluted in the initial fractions was determined to be the camphanic acid ester of (+)-(*R*)-**8** by X-ray crystallographic analysis. By the subsequent hydrolysis with concentrated H_2SO_4 in EtOH, (+)-(*R*)-**8** of 98% ee was recovered. With this (+)-

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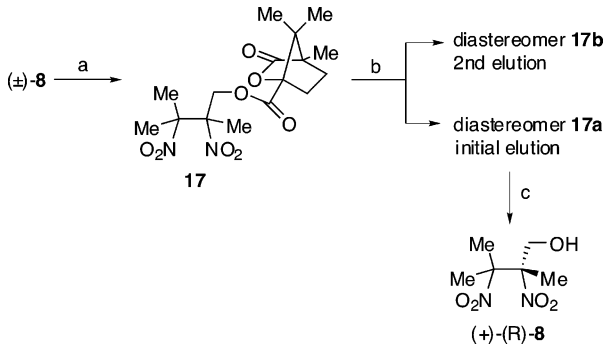
TABLE 2. Magnetic, Optical, and Thermal Properties of 14−16

entry	compd	g-value, a_N (mT)[a]	θ[b] (K), C[c] (emu K/mol)	λ_{max} (nm), $\Delta\epsilon$[d]	mp (°C)[e]
1	(±)-**14**	2.0062, 0.76			*f*
2	(±)-**15**	2.0062, 0.74	−0.72, 0.33 (87)		*f*
3	(*R*)-**15**[g]	2.0062, 0.74	−0.68, 0.33 (89)	259, −1.9 277, +11.2 372, −6.8	*f*
4	(±)-**16a**	2.0064, 0.75	−0.31, 0.37 (99)	-	99.9
5	(±)-**16b**	2.0063, 0.75	−0.69, 0.38 (100)	-	149.6 dec
6	(*R*)-**16b**[g]	2.0063, 0.75	−0.32, 0.35 (92)	292, −12.6 319, +29.5 375, −5.4	126.3
7	(±)-**16c**	2.0062, 0.75	−0.40, 0.37 (98)		89.4
8	(±)-**16d**	2.0062, 0.75	−0.09, 0.36 (96)		134.7
9	(±)-**16e**	2.0062, 0.74	−0.06, 0.33 (88)		95.8

[a] Measured in THF at 25 °C in the external applied magnetic field of 0.5 T. [b] Weiss temperature. [c] Curie constant. Numbers in parentheses denote the estimated spin concentrations (%). [d] CD spectral data measured in THF. [e] Determined by DSC analysis. [f] Obtained as a viscous liquid. [g] 98% ee.

SCHEME 3[a]



[a] Reagents and conditions: (a) (−)-(1*S*,4*R*)-camphanic chloride, *i*-Pr_2NEt, rt, 73%; (b) separation by flash column chromatography on silica gel (hexane/EtOAc 9:1); (c) concentrated H_2SO_4, EtOH, reflux, 76%.

(*R*)-**8**, optically active (*R*)-**15** and (*R*)-**16b** of both 98% ee have been prepared in 30% and 13% overall yields from (*R*)-**9** and (*R*)-**10b**, respectively (Scheme 2). These enantiomeric purities have been determined by HPLC analysis, using a chiral stationary phase (Figure 1).

The CD spectrum of (*R*)-**16b** measured in THF showed a distinct exciton coupling of the two chromophores,[17] i.e., biphenylimidazolyl and phenylbenzoate groups, with positive chirality: a positive first Cotton effect at 319 nm ($\Delta\epsilon = +29.5$) and a negative second one at 292 nm ($\Delta\epsilon = -12.6$) (Figure 2a and Table 2). The same exciton coupling was observed in the solid-state CD spectrum measured in the Nujol mull of (*R*)-**16b** (Figure 2b). These results suggest that the molecular conformation of (*R*)-**16b** is folded both in solution and in the solid state most likely due to the intramolecular $\pi-\pi$ or CH/π interaction between the two biphenyl groups rather than taking a linear structure.

In fact, the most stable molecular conformation of (*R*)-**18**, a model compound of (*R*)-**16b**, optimized by the Monte Carlo method with MMFF force field is a folded structure with positive chirality that is formed by both of the intramolecular $\pi-\pi$ (shortest C(sp^2)···C(sp^2) distance: 3.610 Å) and CH/π (shortest C(sp^2)−H···C(sp^2) distance: 3.210 Å) interactions (Figure 3).

DSC measurement and polarized microscopic observation of (*R*)-**16b** as well as (±)-**16b** showed no sign of the formation of a mesogenic phase. The molecular folding of **16b** in the solid state is most likely to be responsible for the absence of any mesogenic phase.

Conclusions

A combination of a quick reduction of dissymmetric *vic*-dinitro compounds by treatment with Al/Hg and a solvent-free condensation with an aldehyde provides a reliable synthetic procedure for chiral 1,3-dihydroxyimidazolidines which are easily oxidized with aqueous $NaIO_4$ to give the α-NNs with a functionalized and dissymmetric imidazolyl framework. By using this methodology, the optically active α-NNs (*R*)-**15** and (*R*)-**16b** of 98% ee have been prepared from *vic*-dinitro alcohol (+)-(*R*)-**8**, which was obtained by enantiomeric resolution of (±)-**8**. (*R*)-**16b** adopts a folded molecular conformation in the solid state as well as in solution.

Experimental Section

Melting points were determined by differential scanning calorimetry (DSC).

Enantiomeric Resolution of (±)-2,3-Dimethyl-2,3-dinitrobutanol [(±)-8]. To a mixture of (±)-**8** (0.485 g, 2.52 mmol) and (−)-(1*S*,4*R*)-camphanic chloride (0.656 g, 3.03 mmol) in CH_2Cl_2 (20 mL) was added *i*-Pr_2NEt (0.53 mL, 3.0 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 21 h. Then additional (−)-(1*S*,4*R*)-camphanic chloride (0.109 g, 0.51 mmol) and *i*-Pr_2NEt (0.09 mL, 0.51 mmol) were added. The reaction solution was stirred for another 24 h, diluted with aqueous NH_4Cl (40 mL), and extracted with ether (2 × 30 mL). The combined organic phase was washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. The residual solid was washed with ether to provide 0.682 g (73%) of a 1:1 mixture of **17a** (initial fractions, HPLC retention time = 10.1 min) and **17b** (second fractions, HPLC retention time = 12.4 min) as a white solid that was separated by flash column chromatography on silica gel (hexane/EtOAc 9:1), using a UV (254 nm) detector [HPLC analysis conditions; YMC-Pack SIL-06, 0.46 cm × 30 cm, a mixture of hexane and 2-PrOH (9:1) as the mobile phase at the flow rate of 1.0 mL/min, and a UV−vis spectrometer (254 nm) as the detector].

17a: mp 165.1 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 5.19 (d, J = 11.9 Hz, 1H), 4.63 (d, J = 11.9 Hz, 1H), 2.45−2.34 (m, 1H),

(17) (a) *Circular Dichroism Spectroscopy-Exciton Coupling in Organic Stereochemistry*; Harada, N., Nakanishi, K., Eds.; University Science Books: New York, 1983. (b) Berova, N.; Nakanishi, K. In *Circular Dichroism, Principles and Applications*, 2nd ed.; Berova, N., Nakanishi, K., Woody, R., Eds.; Wiley-VCH: New York, 2000; pp 337−382.

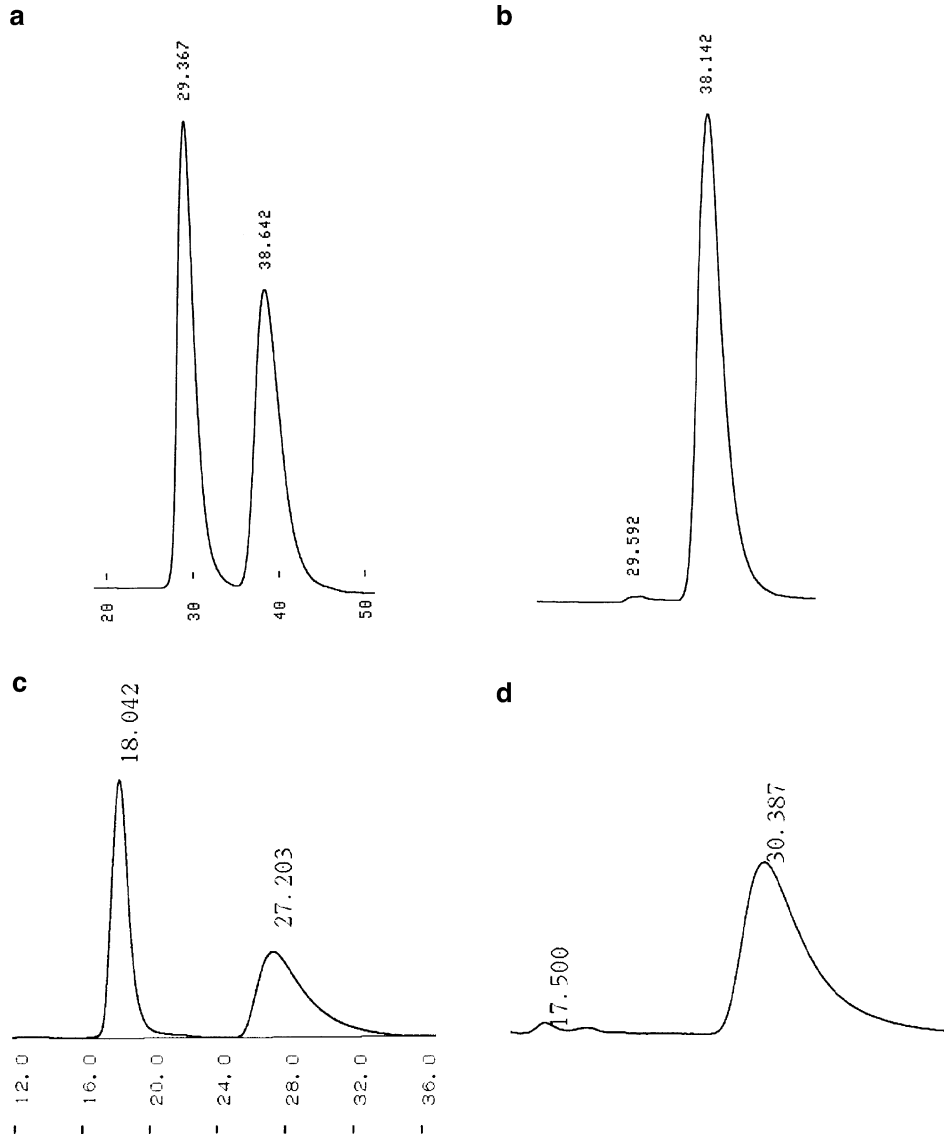


FIGURE 1. HPLC analysis of (a) (±)-**15**, (b) (*R*)-**15** (98% ee), (c) (±)-**16b**, and (d) (*R*)-**16b** (98% ee) carried out by using a chiral stationary-phase column (Daicel Chiralcel OJ and OD-H for **15** and **16**, respectively, 0.46 × 25 cm), a mixture of hexane and 2-PrOH (9:1) as the mobile phase at the flow rate of 0.5 mL/min, and a UV−vis spectrometer (254 nm) as the detector.

2.06−1.87 (m, 2H), 1.83 (s, 3H), 1.76 (s, 3H), 1.72 (s, 3H), 1.69−1.62 (m, 1H), 1.11 (s, 3H), 1.01 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 177.6, 166.4, 92.3, 90.7, 90.4, 66.2, 54.9, 54.5, 30.7, 28.8, 23.2, 23.0, 17.6, 16.7, 16.5, 9.8; IR (KBr) 2974, 2876, 1780, 1761, 1545, 1342, 1263, 1109, 1069 cm^{-1}. Anal. Calcd for $C_{16}H_{24}N_2O_8$: C, 51.61; H, 6.50; N, 7.52. Found: C, 51.63; H, 6.34; N, 7.34.

17b: mp 172.3 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.12 (d, J = 11.9 Hz, 1H), 4.69 (d, J = 11.9 Hz, 1H), 2.33 (ddd, J = 14.8, 13.2, 4.3 Hz, 1H), 2.07−1.86 (m, 2H), 1.83 (s, 3H), 1.76−1.68 (m, 1H), 1.73 (s, 6H), 1.11 (s, 3H), 0.99 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 177.4, 166.2, 92.3, 90.6, 90.4, 66.2, 54.8, 54.4, 30.8, 28.9, 23.2, 23.0, 17.5, 16.7 (two peaks), 9.7; IR (KBr) 2974, 2876, 1790, 1757, 1556, 1547, 1340, 1261, 1105, 1072 cm^{-1}. Anal. Calcd for $C_{16}H_{24}N_2O_8$: C, 51.61; H, 6.50; N, 7.52. Found: C, 52.00; H, 6.32; N, 7.28.

To a solution of **17a** (0.085 g, 0.26 mmol) in EtOH (18 mL) was added a mixture of H_2O (1.2 mL) and H_2SO_4 (1.2 mL). The reaction mixture was heated at reflux for 48 h and concentrated in vacuo. To the residue was added H_2O (20 mL) and the resulting aqueous mixture was extracted with ether (3 × 30 mL). The combined organic phase was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (2:1 hexane/EtOAc) to provide 0.038 g (76%) of (+)-(*R*)-**8** as a white solid.

(+)-(*R*)-8: mp 149.0 °C; $[\alpha]^{25}_D$ +4.7 (*c* 1.0, $CHCl_3$).

General Procedure for Three-Step Conversion of Dissymmetric *vic*-Dinitro Compound (+)-(*R*)-8 to α-Nitronyl Nitroxides, e.g., (+)-(*R*)-2-[4-(4-Octoxyphenyl)-phenyl]-4-[4-(4-octoxyphenyl)benzoyl]oxymethyl-4,5,5-trimethyl-4,5-dihydro-1*H*-imidazolyl-3-oxide-1-oxyl (16b). To a mixture of (*R*)-**8** (0.124 g, 0.645 mmol) and 4-(4-octoxyphenyl)benzoyl chloride (0.223 g, 0.645 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (0.090 mL, 0.645 mmol) and DMAP (0.0080 g, 0.11 mmol). The reaction mixture was stirred at 25 °C for 19 h. Water (20 mL) was added and the aqueous mixture was extracted with ether (3 × 30 mL). The combined organic phase was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (4:1 hexane/EtOAc) to provide 0.180 g (56%) of (*R*)-2,3-dimethyl-2,3-dinitrobutyl 4-(4-octoxyphenyl)benzoate **(10b)** as a white solid.

(+)-(*R*)-**10b**: mp 114.8 °C; $[\alpha]^{21}_D$ +10.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.96 (d, J = 8.6 Hz, 2H), 7.61 (d, J = 8.6 Hz, 2H), 7.54 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 8.6 Hz, 2H), 5.10 (d, J = 11.9 Hz, 1H), 4.96 (d, J = 11.9 Hz, 1H), 4.00

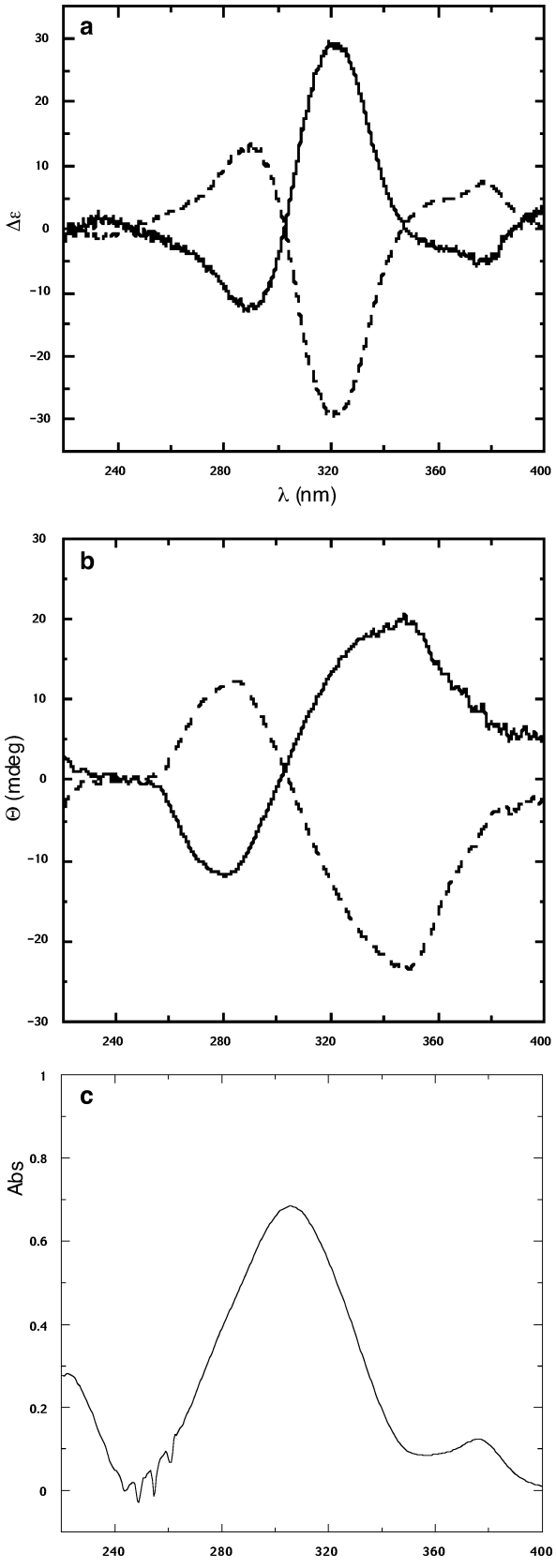


FIGURE 2. CD spectra of (*R*)-**16b** (solid line) and (*S*)-**16b** (dashed line) measured (a) in THF and (b) in the Nujol mull, and (c) UV spectrum of **16b** measured in THF.

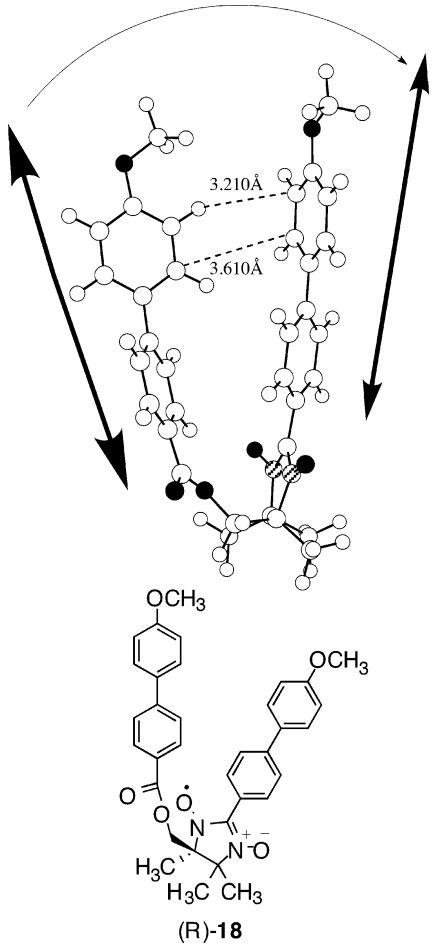


FIGURE 3. The most stable molecular conformation with a folded structure of (*R*)-**18** optimized by the Monte Carlo method with MMFF force field, using Spartan 02.

(t, J = 6.6 Hz, 2H), 1.87 (s, 3H), 1.83−1.78 (m, 2H), 1.79 (s, 3H), 1.78 (s, 3H), 1.47−1.30 (m, 10H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 165.1, 159.5, 146.0, 131.7, 130.1, 128.2, 126.5, 126.4, 114.9, 92.8, 90.6, 68.2, 65.5, 31.9, 29.4, 29.3 (two peaks), 26.1, 23.3, 23.2, 22.7, 17.5, 14.2; IR (KBr) 2920, 2853, 1732, 1605, 1545, 1288, 1273, 1198, 1111, 833, 768 cm^{-1}. Anal. Calcd for $C_{27}H_{36}N_2O_7$: C, 64.78; H, 7.25; N, 5.60. Found: C, 64.80; H, 7.12; N, 5.38.

To aluminum foil (0.046 g, 1.70 mmol) was added 3% aqueous $HgCl_2$ solution (1.0 mL, 0.113 mmol). After the mixture was stirred for 2 min at 25 °C, the liquid portion was removed by a pipet and the residual solid was successively washed with H_2O and THF three times each. After the amalgamated aluminum was covered with THF (2 mL) and cooled to 0 °C, H_2O (0.2 mL) and a solution of (*R*)-**10b** (0.170 g, 0.340 mmol) in THF (2.5 mL) were successively added. The reaction mixture was stirred for 20 min at 0 °C and then filtered on Celite. The filtrate was concentrated in vacuo to give 0.171 g of crude (*R*)-2,3-di(hydroxyamino)-2,3-dimethylbutyl 4-(4-octoxyphenyl)benzoate (**19**) as a white solid.

A mixture of the crude (*R*)-**19** (0.171 g), 4-(4-octoxyphenyl)benzaldehyde (0.105 g, 0.340 mmol), and *p*-TsOH·H_2O (0.0030 g, 0.017 mmol) was stirred with a stirbar for 5 days at 25 °C. To remove the unreacted aldehyde, the mixture was subjected to short flash column chromatography on silica gel (9:1 hexane/EtOAc) to provide 0.085 g [33% from (*R*)-**10b**] of crude (*R*)-1,3-dihydroxy-2-[4-(4-octoxyphenyl)phenyl]-4-[4-(4-octoxyphenyl)benzoyl]oxymethyl-4,5,5-trimethylimidazolidine (**13b**) as a white solid.

A mixture of a $CHCl_3$ solution (10 mL) of the crude (*R*)-**13b** (0.085 g) and an aqueous solution (10 mL) of $NaIO_4$ (0.119 g, 0.556 mmol) was stirred for 25 min at 25 °C. The organic phase

was separated, washed with H_2O (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (9:1 to 4:1 hexane/EtOAc) to give 0.032 g [13% from (*R*)-**10b**] of (*R*)-**16b** as a blue solid.

(*R*)-**16b**: mp 126.3 °C; $[\alpha]^{20}_{435}$ +112.1 (*c* 0.018, THF); IR (KBr) 2924, 2853, 1726, 1603, 1254, 1198, 1097, 824 cm^{-1}. Anal. Calcd for $C_{48}H_{61}N_2O_6$: C, 75.66; H, 8.07; N, 3.68. Found: C, 75.38; H, 8.09; N, 3.41.

Acknowledgment. The authors thank Professor N. Harada and M. Watanabe, Tohoku University, for helpful discussions about the interpretation of the CD spectra.

Supporting Information Available: X-ray crystallographic data in CIF format for compounds (±)-**8** and **17a**; experimental procedures for the preparation of compounds **3a**−**h** and conversion of **5** to (±)-**14**; analytical and spectral data for compounds **3a**−**h**, (±)-**6**−(±)-**9**, (±)-**10a**−**d**, (±)-**14**, (±)-**15**, and (±)-**16a**−**e**; ^1H and ^{13}C NMR spectra for compounds **3a**−**h**, (±)-**6**−(±)-**9**, (±)-**10a**−**d**, and **17a**,**b**, and ^1H NMR spectra of the crude samples for compounds (±)-**11** and (±)-**12**; LRMS (FD) spectra for compounds (±)-**15** and (±)-**16a**,**d**,**e**; HPLC traces for compounds (±)-**15**, (*R*)-**15**, and (±)-**16a**,**d**,**e**; CD and UV spectra of (*R*)-**15** (Figure S1). This material is available free of charge via the Internet at http://pubs.acs.org.

JO0354443