Unexpected Formation of Optically Active 4-Substituted 5-Hydroxy-γ-lactams by Organocatalyzed Reaction of 3-Substituted Cyclobutanones with Nitrosobenzene

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Abstract: An organocatalyzed enantioselective desymmetrization reaction for converting 3-substituted cyclobutanones into 4-substituted 5-hydroxy-γ-lactams is presented. This involves a ring-expanding *O*-nitroso aldol–cyclization domino sequence. This synthetic protocol provides access to five-membered ring systems in good yields with the generation of two new stereogenic centers.

Key words: rearrangements, ring expansion, ketones, organocatalysis

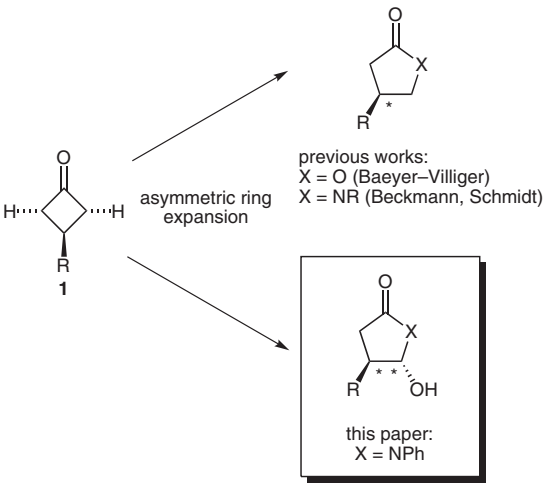
Cyclobutanones reveal interesting characteristics such as high electrophilicity and ring strain which make them good substrates for ring-transformation reactions. Functionalized cyclobutanones have been the subject of studies which describe their reactivity with nucleophiles to induce ring opening, ring contraction, and ring expansion.[1]

Synthetically important ring-expansion reactions include those that add the elements of carbon, oxygen, or nitrogen to an existing carbocyclic unit.[2] These reactions can be viewed as the formal insertion of a group into a carbon–carbon single bond. When a prochiral cyclobutanone such as **1** is employed in such a reaction, the potential of carrying out asymmetric ring-expansion chemistry arises (Scheme 1).

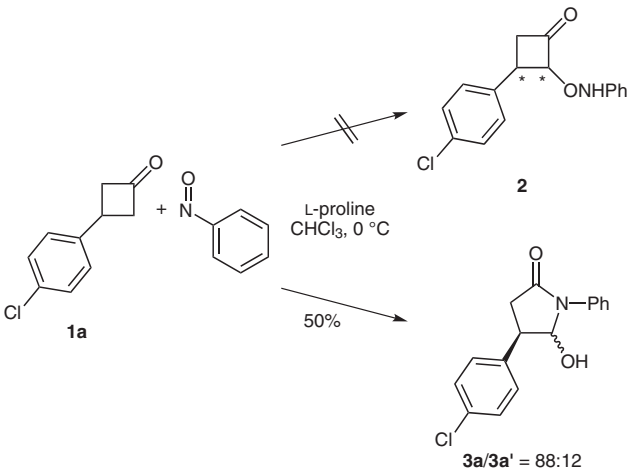
Asymmetric Baeyer–Villiger processes using enzymatic,[3] metal-promoted,[4] and organocatalyzed[5] reactions or Beckmann[6] and Schmidt reactions[2e] have received the greatest share of attention in this regard.

Following our involvement in the chemistry of small carbocylic derivatives,[7] we were intrigued by the possibility of preparing optically active 2,3-disubstituted cyclobutanones by an enantio- and diastereoselective organocatalytic[8] desymmetrization of 3-substituted prochiral cyclobutanones.

During this research, initially we decided to examine the reaction of suitable prochiral cyclobutanones **1** with nitrosobenzene in the presence of different organocatalysts[9] (Scheme 2).



Scheme 1



Scheme 2 Attempted synthesis of α-aminoxylated cyclobutanone **2**

The preliminary reaction of **1a** with nitrosobenzene (3.0 equiv) in the presence of 30% L-proline gave, instead of the expected α-aminoxylated cyclobutanone **2**, good yields (50%) of the α-hydroxy-γ-lactam **3** as a mixture of two diastereomers **3a/3a′** (dr = 88:12), that we considered, at this stage, to be a *trans*/*cis* mixture (44% and 70% ee, respectively) of a single regioisomer.

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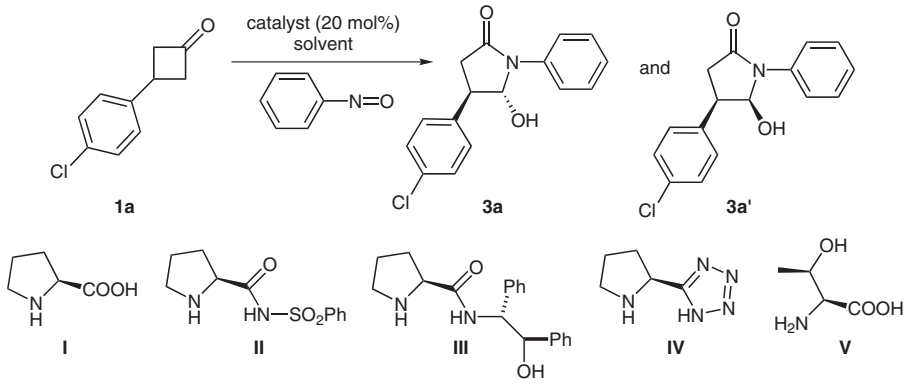
Table 1 Optimization Studies[a]



Entry	Catalyst	Solvent	Temp (°C)	Yield (%)[b]	ee *trans* (%)[c]	dr (%)[d] *trans/cis*
1[e]	**I**	$CHCl_3$	0	50	44	88:12
2[f]	**I**	$CHCl_3$	0	65	50	70:30
3	**II**	$CHCl_3$	0	40	52	>99:<1
4	**II**	$CHCl_3$	–10	30	>99	>99:<1
5	**II**	$CHCl_3$	–20	–	–	–
6	**III**	$CHCl_3$	0	–	–	–
7	**III**	toluene	0	–	–	–
8	**IV**	$CHCl_3$	0	55	58	>99:<1
9	**IV**	CH_2Cl_2	0	30	60	>99:<1
10	**IV**	DMSO	r.t.	0	–	–
11	**IV**	DMF	0	0	–	–
12	**IV**	toluene	0	0	–	–
13	**V**	$CHCl_3$	0	0	–	–

[a] Unless otherwise noted, all the reactions were carried out with 3.0 equiv of nitrosobenzene relative to prochiral cyclobutanone and 20 mol% of catalyst at 0 °C for 96 h.
[b] Yield of isolated product (sum of diastereomers).
[c] Determined by chiral HPLC analysis.
[d] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.
[e] 30 mol% of L-proline was used.
[f] The reaction was carried out by slow addition (48 h) of nitrosobenzene to 5 equiv of cyclobutanone **1** in the presence of 30 mol% of L-proline.

This was an unprecedented result and its importance was further increased by the fact that 2-pyrrolidinones and their derivatives are very interesting compounds for the pharmaceutical industry.[10] Moreover the 5-hydroxy-substituted 2-pyrrolidinones show several versatile applications[11] and are also the precursors of the highly reactive cyclic α-acyliminium ion.[12]

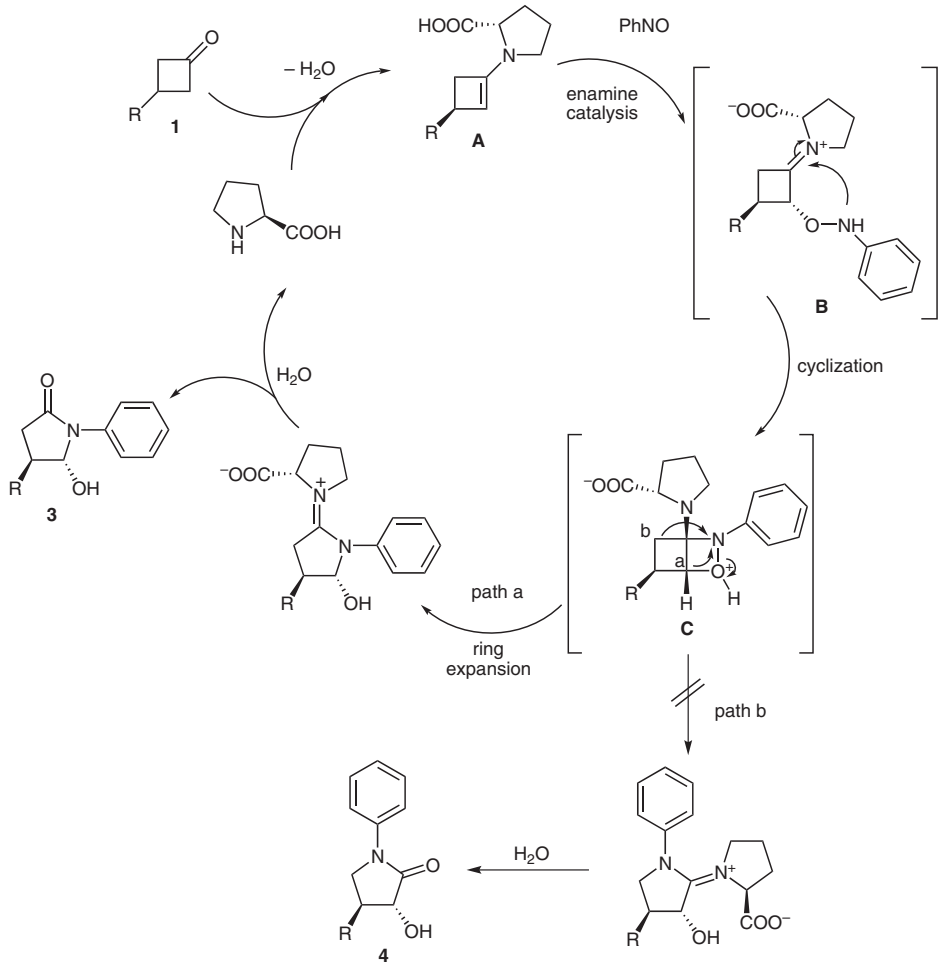
Intrigued by this preliminary result, we sought to establish reaction conditions that would give improvement in yield and stereoselectivity.

The reaction of cyclobutanone **1a** and nitrosobenzene was investigated as a model and the effect of a number of known catalysts **I**–**V**, different solvents, and reaction conditions were examined with the results summarized in Table 1.

Among the catalysts probed, **I** and **IV** were the best promoters of the process (Table 1, entries 2 and 8) in terms of both chemical yield and stereoselectivity. As the use of other solvents as well as reaction temperatures was not advantageous, we extended this reaction to different cyclobutanones **1b**–**g** using $CHCl_3$ as a solvent at 0 °C, and the results are summarized in Table 2.

The reaction can be rationalized by assuming the mechanism shown in Scheme 3, based on a catalytic cycle through a cascade reaction initiated by an *O*-nitroso aldol–cyclization domino reaction resulting in a cyclobutyl ring expansion.

Chiral L-proline catalyzes the diastereospecific in situ generation of enamine **A** from cyclobutanone **1**. Subsequent nucleophilic addition to nitrosobenzene furnishes



Scheme 3 Proposed catalytic cycle of the domino organocatalytic asymmetric synthesis of γ-lactams **3** (only the *trans*-isomer is shown)

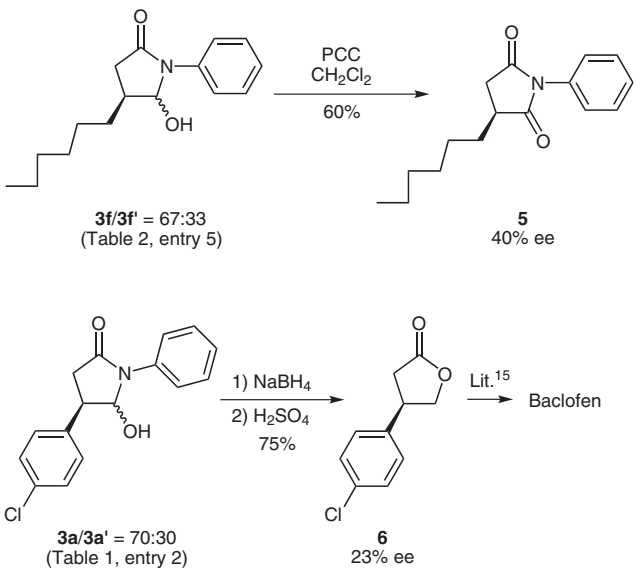
the α-aminoxylated cyclobutyl iminium intermediate **B**. This intermediate undergoes intramolecular nucleophilic 1,2-addition followed by rearrangement of the bicyclic intermediate **C**, either into the 5-hydroxy-γ-lactam **3** by migration of the more substituted terminus (path a) or into the 3-hydroxy-γ-lactam **4** by migration of the less substituted terminus (path b).[13]

On the basis of this mechanism we could be dealing either with two geometric isomers of a single regioisomer or with two regioisomers with the same geometry. To solve the above-mentioned uncertainty we carried out the oxidation of the inseparable mixture of diastereomers **3f** and **3f′** (Scheme 4).

The fact that we obtained only the product **5** (ee = 40%) was taken as a conclusive evidence that mixture **3f/3f′** was a *trans*/*cis* mixture of a single regioisomer (5-hydroxy-γ-lactams).

The geometry of compounds **3a**–**g** and **3a′**–**g′** was assigned on the basis of the value of the coupling constants for C4–H and C5–H as well as by comparison with literature data.[14]

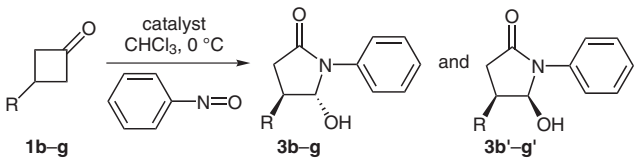
On the other hand, the absolute stereochemistry of the major isomer of compounds **3a**–**g** could be assigned by analogy with that assigned to **3a/3a′** after its conversion into



Scheme 4 Reactions of two γ-lactams **3** to assign their relative and absolute configurations. Only the prevailing stereochemistry is shown.

the (*R*)-lactone **6** (ee = 23%) that is a known precursor[15] of the amino acid Baclofen (Scheme 4).

Table 2 Asymmetric Synthesis of 4-Substituted 5-Hydroxy-γ-lactams **3**[a]



Entry	R (product)	Catalyst	Yield[b]	ee *trans* (%)[c]	dr(%)[d] *trans/cis*
1	Ph (**3b/3b′**)	**I**	40	20	95:5
		IV	45	30	79:21
2	4-BrC_6H_4 (**3c/3c′**)	**I**	57	27	73:27
		IV	20	4	>99:<1
3	4-MeC_6H_4 (**3d/3d′**)	**IV**	30	40	77:23
4	$PhCH_2CH_2$ (**3e/3e′**)	**I**	65	51	93:7
		IV	40	42	94:6
5	C_6H_{13} (**3f/3f′**)	**I**	60	38	67:33
		IV	40	60	99:1
6	*c*-Hex (**3g/3g′**)	**I**	48	37	85:15
		IV	41	56	72:28

[a] The reactions were carried out in $CHCl_3$, with 3.0 equiv of nitrosobenzene relative to prochiral cyclobutanone and 20 mol% of catalyst **IV** or by slow addition (48 h) of nitrosobenzene to 5 equiv of cyclobutanone **1** in the presence of 30 mol% of L-proline, at 0 °C for 96 h.
[b] Yield of isolated product (sum of diastereomers).
[c] Determined by chiral HPLC analysis.
[d] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

In summary we have developed an organocatalyzed desymmetrization of 3-substituted cyclobutanones using as electrophile nitrosobenzene that led to the discovery of the first direct organocatalyzed enantioselective 'ring-expanding *O*-nitroso aldol–cyclization domino reaction'.

Two are the focal points of this reaction sequence: a) for the first time, we could successfully combine enamine organocatalysis with a cyclization–ring-expansion-terminated reaction in a tandem sequence,[16] b) the fundamental role of the strained cyclobutyl ring that easily expands to create the pyrrolidinone derivatives. This is a powerful approach for the generation of these optically active nitrogen-containing molecules.[17]

Despite the moderate enantioselectivities, our results add new knowledge because the mechanistic model proposed represents an extension for existing concepts in the chemistry of cyclobutanes and enamine catalysis. Further efforts will be spent on evaluating the scope of this processes and the improvement of stereochemistry.

Acknowledgment

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(17) **General Procedure (Using Catalyst I)**

To a $CHCl_3$ (2.7 mL) solution of the prochiral cyclobutanone **1** (3 mmol) and L-proline (0.18 mmol) was added a $CHCl_3$ (0.9 mL) solution of nitrosobenzene (0.6 mmol) over 48 h at 0 °C via syringe pump, and the mixture was stirred for 96 h at that temperature. The crude reaction mixture was directly loaded on silica gel column without workup, and pure products were obtained by flash column chromatography (silica gel, hexane–Et_2O).

General Procedure (Using Catalyst IV)

In a glass vial equipped with a magnetic stirring bar, to 0.375 mmol of the prochiral cyclobutanone **1**, catalyst **IV** (0.075 mmol, 20 mol%) was added, and the reaction mixture was stirred at ambient temperature for 10–15 min. To the reaction mixture nitrosobenzene (1.13 mmol) was added and stirred at 0 °C for the time indicated in Tables 1 and 2. The crude reaction mixture was directly loaded on silica gel column without workup, and pure products were obtained by flash column chromatography (silica gel, mixture of hexane–Et_2O).

4-(4-Chlorophenyl)-5-hydroxy-1-phenylpyrrolidin-2-one (3a)

Yield 60%; yellow oil. IR (film): ν = 3400, 1650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.68 (dd, 1 H, *J* = 4.5, 14.1 Hz), 2.93 (t, 1 H, *J* = 14.4 Hz), 3.26–3.33 (m, 1 H), 5.48 (d, 1 H, *J* = 5.4 Hz), 7.18–7.72 (m, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.9, 47.86, 103.2, 120.0, 125.6, 128.6, 128.7, 129.2, 133.6, 137.6, 139.3, 169.8. MS: *m/z* (%) = 269 (100) [M^+ – 18], 240 (80), 206 (17), 136 (23), 104 (72). The ee was determined to be 58% ee by chiral-phase HPLC using a Daicel Chiralcel OJ column (hexane–*i*-PrOH = 80:20, flow rate 1.2 mL/min, λ = 254 nm): t_R(major) = 12.1 min; t_R(minor) = 14.4 min.

5-Hydroxy-1,4-diphenylpyrrolidin-2-one (3b/3b′)

Spectral data refer to a 95:5 inseparable mixture of two *trans*- and *cis*-diastereomers. Yield 40%; yellow oil. IR (film): ν = 3400, 1650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.58–2.66 (m, 1 H), 2.74–2.81 (m, 1 H), 2.90 (t, 1 H, *J* = 14.1 Hz), 3.05 (t, 1 H, *J* = 13.8 Hz), 3.14–3.20 (m, 1 H), 3.23–3.30 (m, 1 H), 4.58 (br s, 1 H), 4.92 (t, 1 H), 5.48 (d, 1 H, *J* = 5.4 Hz), 5.55 (dd, 1 H, *J* = 7.05, 9.6 Hz), 6.74–7.73 (m, 20 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.1, 38.6, 48.5, 48.8, 92.4, 103.5, 114.6, 118.8, 120.1, 124.9, 125.5, 127.0, 127.2, 127.6, 127.8, 128.5, 128.6, 129.0, 129.1, 129.3, 139.3, 139.5, 170.3, 170.8. MS: *m/z* (%, the same for the two diastereomers) = 235 (100) [M^+ – 18], 206 (100), 115 (20), 104 (48), 77 (57), 63 (7), 51 (16). The ee was determined to be 20% ee for the *trans*-diastereomer by chiral-phase HPLC using a Daicel Chiralcel OJ column (hexane–*i*-PrOH = 90:10, flow rate 1.2 mL/min, λ = 254 nm): t_R(major) = 30.8 min; t_R(minor) = 36.6 min.

5-Hydroxy-4-phenethyl-1-phenylpyrrolidin-2-one (3e)

Spectral data worked out from the 94:6 inseparable mixture of two *trans*- and *cis*-diastereomers **3e/3e′**. Yield 65%; orange oil. IR (film): ν = 3350, 1660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.77–2.14 (m, 3 H), 2.36–2.57 (m, 2 H), 2.71 (t, 2 H, *J* = 7.5 Hz), 3.41 (br s, 1 H), 5.29 (d, 1 H, *J* = 5.1 Hz), 7.13–7.69 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.9, 36.0, 42.2, 52.3, 102.7, 119.9, 126.1, 128.2, 128.4, 128.5, 128.6, 139.6, 140.9, 170.4. MS: *m/z* (%, the same for the two diastereomers) = 263 (31) [M^+ – 18], 172 (100), 106 (14), 91 (60), 77 (27), 65 (10), 51 (8). The ee of the *trans*-diastereomer was determined to be 51% ee by chiral-phase HPLC using a Daicel Chiralcel OJ column (hexane–*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 254 nm): t_R(major) = 26.1 min; t_R(minor) = 33.6 min.

4-Hexyl-5-hydroxy-1-phenylpyrrolidin-2-one (3f/3f′)

Spectral data refer to a 67:33 inseparable mixture of two *trans*- and *cis*-diastereomers. Yield 60%; orange oil. IR (film): ν = 3400, 1660 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84–1.59 (m, 26 H), 1.92–2.06 (m, 2 H), 2.27–2.63 (m, 4 H), 4.73 (d, 1 H, *J* = 9.3 Hz), 5.17 (d, 1 H, *J* = 4.8 Hz), 5.22 (dd, 1 H, *J* = 6.9, 9.3 Hz), 6.76–7.72 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.5, 26.6, 26.8, 29.1, 31.6, 33.0, 33.8, 36.1, 37.3, 42.7, 43.3, 91.4, 102.8, 114.5, 118.6, 119.9, 125.2, 128.5, 129.3, 139.7, 144.1, 170.7, 171.0. MS: *m/z* (%, the same for the two diastereomers) = 243 (77) [M^+ – 18], 172 (100), 158 (26), 130 (14), 104 (24), 77 (33). The ee was determined to be 38% ee for the *trans*-diastereomer and 44% ee for the *cis*-diastereomer by chiral-phase HPLC using a Daicel Chiralcel OJ column (hexane–*i*-PrOH = 95:5, flow rate 0.8 mL/min, λ = 254 nm): *trans*-diastereomer: t_R(minor) = 14.3 min(minor); t_R(major) = 17.4 min; *cis*-diastereomer: t_R(major) = 22.2 min; t_R(minor) = 26.9 min.

Procedure for the Synthesis of 3-Hexyl-1-phenylpyrrolidine-2,5-dione (5)

PCC (85.1 mg, 0.395 mmol) was added to a solution of compounds **3f/3f′** (dr = 67:33; 70 mg, 0.270 mmol) in CH_2Cl_2 (8 mL), the mixture was then stirred at r.t. for 2 h. The reaction mixture was filtered through a Celite pad, concentrated to give the crude mixture, which was then purified by flash column chromatography (hexane–Et_2O = 3:1) on silica gel to give the pure pyrrolidine-2,5-dione **5**. Yield 60%; yellow oil. IR (film): ν = 1774,1701, 1443, 1376 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.83–1.45 (m, 10 H), 1.58–1.68 (m, 2 H), 1.95–2.03 (m, 1 H), 2.50–2.61 (m, 1 H), 2.91–3.05 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.5, 26.6, 28.9, 29.6, 31.51, 31.54, 34.5, 40.0, 126.4, 128.5, 129.1, 131.9, 175.6, 178.9. MS: *m/z* (%) = 259 (10) [M^+], 188 (35), 175 (100), 147 (10), 119 (30), 93 (16), 77 (7), 55 (14). The ee was determined to be 40% ee by chiral-phase HPLC using a Daicel Chiralcel OJ column (hexane–*i*-PrOH = 95:5, flow rate 1.2 mL/min, λ = 254 nm): t_R(major) = 41.8 min; t_R(minor) = 44.8 min.