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Synthesis of Hydantoins from Enantiomerically Pure α-Amino Amides without Epimerization

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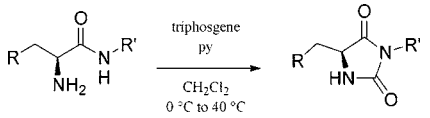
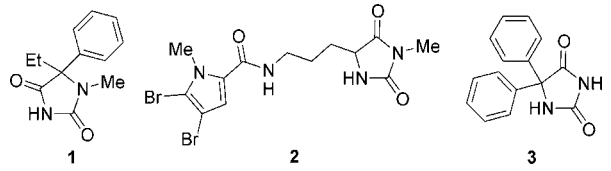


A method for the preparation of enantiomerically pure hydantoins from optically pure α-amino amides utilizing triphosgene is described. We also propose that the racemization observed with 1,1′-carbonyldiimidazole (CDI) for this type of reaction is due to the imidazole carbamate intermediates.

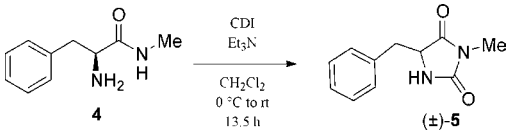
Hydantoins[1] are an important structural moiety found in several natural products, including (−)-deltoin, **1**,[2] and midpacamide, **2**,[3] as well as many biologically active and therapeutically useful compounds, such as phenytoin, **3**, utilized for the treatment of seizures.[4] In addition, hydantoins can serve as useful intermediates in the synthesis of amino acids employing hydantoinases and other related biocatalysts.[5]



1 **2** **3**

Recently, in the course of conducting a structure−activity relationship (SAR) study, attempts to prepare hydantoin (*S*)-**5** by cyclizing α-amino amide **4** in the presence of 1,1′-carbonyldiimidazole (CDI) were made (Scheme 1).[6] Although cyclization did proceed as expected, complete racemization was observed.[7,8] Bis(4-nitrophenyl)carbonate[9] and 4-nitrophenyl chloroformate[10] have been reportedly employed in place of CDI for this type of transformation with good stereochemical integrity. However, some difficulty can be realized in the separation of the desired hydantoin products from the byproduct, 4-nitrophenol. Nowick and co-workers reported that when peptides were subjected to treatment with a toluene solution of phosgene and pyridine in dichloromethane (DCM) peptide isocyanates were produced along with variable quantities (∼20%) of the corresponding hydantoins.[11] Utilizing modified Schotten−Baumann conditions, they were able to minimize the production of hydantoins in favor of the peptide isocyanates. Herein, we report methodology for the conversion of enantiomerically pure α-amino amides to hydantoins without epimerization.

SCHEME 1



4 (±)-**5**

Initially, we suspected that the presence of base (Et_3N) was responsible for the observed racemization. However, when the reaction was conducted with CDI in the absence of base some racemization still occurred, reducing the enantiomeric excess to 70% (Table 1, entry 2). In addition, the reaction was sluggish and only gave the hydantoin product in 50% yield. Next, we sought an alternative coupling reagent for CDI. Triphosgene, a useful substitute to phosgene, was selected.[12] Gratifyingly, this coupling reagent resulted in cyclization of **4** to give enantiomerically pure hydantoin **5** (entries 3−5).[13] Utilization of 0.4 equiv of triphosgene was optimum. Several bases were also

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(1) For a recent review of hydantoin chemistry, see: Meusel, M.; Gütschow, M. *Org. Prep. Proced. Int*. **2004**, *36*, 391−443.

(2) Chen, I.-S.; Chang, C.-T.; Sheen W.-S.; Teng, C.-M.; Tsai, I.-L.; Duh, C. Y.; Ko, F. N. *Phytochemistry* **1996**, *41*, 525−530.

(3) (a) Jimenez, C.; Crews, P. *Tetrahedron Lett*. **1994**, *35*, 1375−1378. (b) Fathi-Afshar, R.; Allen, T. M. *Can J. Chem*. **1988**, *66*, 45−50. (c) Chevolot, L.; Padua, S.; Ravi, B. N.; Blyth, P. C.; Scheuer, P. J. *Heterocycles* **1977**, *7*, 891−894.

(4) McNamara, J. O. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics, Tenth Edition*; Hardman, J. G., Limbird, L. E., Eds.; McGraw-Hill: New York, 2001; Chapter 21, pp 528−531.

(5) Altenbuchner, J.; Siemann-Herzberg, M.; Syldatk, C. *Curr. Opin. Biotechnol*. **2001**, *12*, 559−563.

(6) (a) Kim, D.; Wang, L.; Caldwell, C. G.; Chen, P.; Finke, P. E.; Oates, B.; MacCoss, M.; Mills, S. G.; Malkowitz, L.; Gould, S. L.; DeMartino, J. A.; Springer, M. S.; Hazuda, D.; Miller, M.; Kessler, J.; Danzeisen, R.; Carver, G.; Carella, A.; Holmes, K.; Lineberger, J.; Schleif, W. A.; Emini, E. A. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 3099−3102. (b) de Laszlo, S. E.; Allen, E. E.; Li, B.; Ondeyka, D.; Rivero, R.; Malkowitz, L.; Molineaux, C.; Siciliano, S. J.; Springer, M. S.; Greenlee, W. J.; Mantlo, N. *Bioorg. Med. Chem. Lett*. **1997**, *7*, 213−218. (c) Lewis, R. T.; Macleod, A. M.; Merchant, K. J.; Kelleher, F.; Sanderson, I.; Herbert, R. H.; Cascieri, M. A.; Sadowski, S.; Ball, R. G.; Hoogsteen, K. *J. Med. Chem*. **1995**, *38*, 923−933.

(7) (a) Nefzi, A.; Giulianotti, M.; Truong, L.; Rattan, S.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem*. **2002**, *4*, 175−178. (b) Nomoto, Y.; Takai, H.; Hirata, T.; Teranishi, M.; Ohno, T.; Kubo, K. *Chem. Pharm. Bull*. **1990**, *38*, 3014−3019.

(8) For a recent example of a solid-phase method for the preparation of enantiomerically pure hydantoins utilizing CDI, see: Vázquez, J.; Royo, M.; Albericio, F. *Lett. Org. Chem*. **2004**, *1*, 224−226.

(9) Izdebski, J.; Pawlak, D. *Pol. J. Chem*. **1997**, *71*, 1066−1074.

(10) (a) Yamaguchi, J.; Harada, M.; Kondo, T.; Noda, T.; Suyama, T. *Chem Lett*. **2003**, *32*, 372−373. (b) Itoh, F.; Nishikimi, Y.; Hasuoka, A.; Yoshioka, Y.; Yukishige, K.; Tanida, S.; Aono, T. *Chem. Pharm. Bull*. **1998**, *46*, 255−273.

(11) Nowick, J. S.; Holmes, D. L.; Noronha, G.; Smith, E. M.; Nguyen, T. M.; Huang, S.-L. *J. Org. Chem*. **1996**, *61*, 3929−3934.

(12) Eckert, H.; Forster, B. *Angew. Chem., Int. Ed. Engl*. **1987**, *26*, 894−895.

(13) The enantiomeric excess of the products were determined by ^{1}H NMR spectroscopy using the chiral shift reagent Pr(hfc)$_3$. This method could accurately measuring 2% of the minor isomer.

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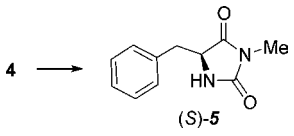
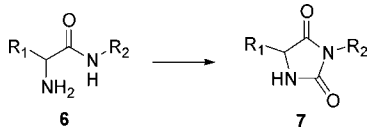
TABLE 1. Effect of Reagents on the Formation of Hydantoin 5[14a] from α-Amino Amide 4

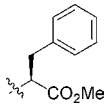


entry	reagent	base	yield, %	ee, %
1	CDI[a]	Et_3N	55−75	0
2	CDI[a]		50	70
3	triphosgene[b]	Et_3N	30	>96
4	triphosgene[b]	imidazole	42	>96
5	triphosgene[b]	pyridine	71	>96

[a] CDI (10 equiv), CH_2Cl_2, Ar atm, 0 °C to rt for 13.5 h. [b] Triphosgene (0.4 equiv), CH_2Cl_2, Ar atm, 0 °C for 1.5 h then 40 °C for 12 h.

TABLE 2. Preparation of Hydantoins 7 from α-Amino Amides 6[a]



entry	R_1	R_2	product	yield, %	ee, %
1	$PhCH_2$	CH_2CH_3	(*S*)-**7a**[15b]	73	>96
2	$PhCH_2$	$(CH_2)_3CH_3$	(*S*)-**7b**	70	>96
3	$PhCH_2$	CH_2Ph	(*S*)-**7c**[15c]	58	>96
4	$PhCH_2$	$(CH_2)_2$-*p*-OMe-Ph	(*R*)-**7d**	41	>96
5	$(CH_3)_2CHCH_2$	CH_2Ph	(*S*)-**7e**	55	>96
6	$TBSOCH_2$	CH_2Ph	(*R*)-**7f**	73	>96
7	$PhCH_2$		(*S*,*S*)-**7g**	80	*c*

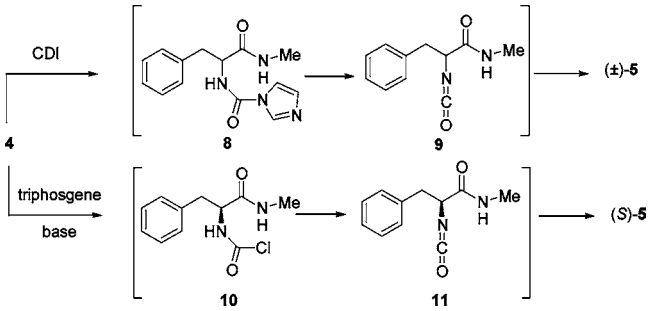
[a] Triphosgene (0.4 equiv), CH_2Cl_2, Ar atm, 0 °C for 1.5 h then 40 °C for 12 h. [b] HCl salt of **6g** was used. [c] de > 96%.

evaluated in this reaction with pyridine proving best. Finally, the highest yields were obtained when the reaction mixture was initially stirred at 0 °C for 1.5 h and then at 40 °C for 12 h.

The scope of the reaction was evaluated utilizing a variety of α-amino amides **6** (Table 2). These substrates were generally prepared directly from the corresponding amino acid methyl esters. In the case of (*R*)-**6d**, (*R*)-*N*-BOC-phenylalanine methyl ester was allowed to react with 2-(4-methoxyphenyl)ethylamine followed by removal of the BOC protecting group with trifluoroacetic acid in DCM. Also, (*R*)-**6f** was prepared from D-serine methyl ester by first protecting the alcohol with *tert*-butyldimethylsilyl chloride and imidazole in DMF followed by treatment with benzylamine in methanol. Cyclization of the α-amino amides **6** with triphosgene (0.4 equiv) in the presence of pyridine gave hydantoins **7** in moderate isolated yields (41−80%) and in excellent optical purities (>96% ee).[14]

Treatment of **4** with CDI or triphosgene/base presumably gives intermediates **8** and **10**, respectively (Scheme 2). These intermediates can proceed to generate isocyanates. Both reagents have previously been utilized to produce isolable aliphatic

SCHEME 2



isocyanates.[16] Intermediates similar to **10**[11,17] and amino acid ester isocyanates[16b] have been shown to be stable from racemization in the presence of base. Finally, cyclization of **9** and **11** gives the observed hydantoins (±)-**5** and (*S*)-**5**, respectively. The intermediate imidazole carbamate **8** is therefore responsible for the observed racemization seen with CDI resulting in (±)-**5**.

In summary, method for the preparation of enantiomerically pure hydantoins from optically pure α-amino amides utilizing triphosgene was developed. We also propose that the racemization observed with CDI in this type of reaction is due to the imidazole carbamate intermediates.

Experimental Section

General Procedure for the Preparation of α-Amino Amides 4 and 6a−c,e. A solution of the amino acid methyl ester hydrochlorides (2 mmol) and the alkylamines (20 mmol) in anhydrous methanol (10 mL) was stirred at room temperature for 3 days. The reaction mixture was concentrated, and the residue was purified by column chromatography on silica gel using ethyl acetate/methanol (96:4) as eluant to give the α-amino amides **4**, **6a−c**,**e**.

(*S*)-2-Amino-*N*-methyl-3-phenylpropionamide (4).[18a] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (t, 2H, J = 7.5 Hz), 7.27−7.22 (m, 4H), 3.61 (dd, 1H, J = 4.0, 9.5 Hz), 3.30 (dd, 1H, J = 4.0, 13.5 Hz), 2.83 (d, 3H, J = 7.5 Hz), 2.67 (dd, 1H, J = 9.5, 13.5 Hz), 1.38 (brs, 2H).

(*S*)-2-Amino-*N*-ethyl-3-phenylpropionamide (6a).[18b] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (t, 2H, J = 7.5 Hz), 7.27−7.22 (m, 4H), 3.61 (dd, 1H, J = 4.0, 9.0 Hz), 3.33−3.27 (m, 3H), 2.69 (dd, 1H, J = 9.0, 13.5 Hz), 1.56 (brs, 2H), 2.67 (t, 3H, J = 7.5 Hz).

(*S*)-2-Amino-*N*-butyl-3-phenylpropionamide (6b).[18c] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (t, 2H, J = 7.0 Hz), 7.26−7.22 (m, 4H), 3.60 (dd, 1H, J = 4.5, 9.5 Hz), 3.29−3.23 (m, 3H), 2.70 (dd, 1H, J = 9.5, 13.5 Hz), 1.50−1.29 (m, 6H), 0.92 (t, 3H, J = 7.5 Hz).

(*S*)-2-Amino-*N*-benzyl-3-phenylpropionamide (6c).[18d] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (s, 1H), 7.34−7.21 (m, 10H), 4.44 (m, 2H), 3.70 (dd, 1H, J = 4.5, 9.5 Hz), 3.29 (dd, 1H, J = 4.5, 13.5 Hz), 2.70 (dd, 1H, J = 9.5, 13.5 Hz), 1.70 (brs, 2H).

(14) Cyclization of **6c** with CDI in CH_2Cl_2 gave racemic **7c**. Cyclization of **6g** (HCl salt) with CDI in DMF in the presence of DIPEA gave **7g** as a mixture of diastereomers resulting from epimerzation of the hydantoin.

(15) (a) Lazarus, R. A. *J. Org. Chem.* **1990**, *55* (15), 4755−4757. (b) Wolfe, S.; Bowers, R. J.; Shin, H. S.; Sohn, C. K.; Weaver, D. F.; Yang, k. *Can. J. Chem.* **1988**, *66*, 2751−2762. (c) Zhai, Z.; Chen, J.; Wang, H.; Zhang, Q. *Synth. Commun.* **2003**, *33* (11), 1873−1883.

(16) (a) Takeda, Y.; Kawagoe, K.; Yokomizo, A.; Yokomizo, Y.; Hosokami, T.; Ogihara, Y.; Yokohama, S. *Chem. Pharm. Bull.* **1998**, *46*, 434−444. (b) Nowick, J. S.; Powell, N. A.; Ngugen, T. M.; Noronha, G. *J. Org. Chem.* **1992**, *57*, 7364−7366.

(17) Chong, P. Y.; Petillo, P. A. *Tetrahedron Lett.* **1999**, *40*, 2493−2496.

(18) (a) Ojima, I.; Chen, H. J. C.; Qiu, X. G. *Tetrahedron* **1988**, *44*, 5307−5718. (b) Suzuki, K.; Fujita, H.; Sasaki, Y.; Shiratori, M.; Sakurada, S.; Kisara, K. *Chem. Pharm. Bull.* **1988**, *36*, 4834−4840. (c) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755−756. (d) Conley, J. D.; Kohn, H. *J. Med. Chem.* **1987**, *30*, 567−574. (e) Evans, B. E.; Rittle, K. E.; Homnick, C. F.; Springer, J. P.; Hirshfield, J.; Veber, D. F. *J. Org. Chem.* **1985**, *50*, 4615−4625.

(*S*)-2-Amino-4-methylpentanoic Acid Benzylamide (6e).[18e] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.33 (t, 2H, J = 7.0 Hz), 7.29−7.26 (m, 3H), 4.45 (d, 2H, J = 6.0 Hz), 3.45 (dd, 1H, J = 4.0, 10.0 Hz), 1.80−1.73 (m, 2H), 1.56 (brs, 2H), 1.38 (m, 1H), 0.97 (d, 3H, J = 7.0 Hz), 0.94 (d, 3H, J = 6.0 Hz).

(*R*)-2-Amino-*N*-[2-(4-methoxyphenyl)ethyl]-3-phenylpropionamide (6d). A solution of (*R*)-*N*-BOC-phenylalanine methyl ester (0.43 g, 1.54 mmol) and 2-(4-methoxy phenyl)ethylamine (1.5 g, 10 mmol) in anhydrous methanol (5 mL) was stirred at room temperature for 3 d. After removal of the solvent, the residue was purified by column chromatography on silica gel using hexane/ethyl acetate (70:30) as eluant to give (*R*)-2-*N*-BOC-amino-*N*-[2-(4-methoxyphenyl)ethyl]-3-phenylpropionamide as a light yellow solid (325 mg, 53%).: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (t, 2H, J = 7.5 Hz), 7.25 (m, 1H), 7.18 (d, 2H, J = 7.0 Hz), 6.93 (d, 2H, J = 8.5 Hz), 6.79 (d, 2H, J = 8.0 Hz), 5.62 (brs, 1H), 5.01 (brs, 1H), 4.23 (brs, 1H), 3.78 (s, 3H), 3.42−3.30 (m, 2H), 3.10−2.95 (m, 2H), 2.67−2.50 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 171.1, 158.5, 130.7, 129.8, 129.6, 128.9, 127.2, 114.3, 55.5, 41.0, 39.0, 34.8, 28.5. Mp: 139−140 °C. $[\alpha]^{24.3}_D$ = −1.6 (*c* 0.5, MeOH). FT-IR (KBr pellet, ν_{max}, cm^{-1}): 3348s, 3323s, 2971m, 2827m, 1686s, 1652s, 1548s, 1514s, 1246s, 1169s, 1031m, 820m, 765m, 703m. HRESMS [M + H]$^+$: 399.2286 (calcd for [$C_{23}H_{30}N_2O_4$ + H]$^+$, 399.2284).

Next, a solution of (*R*)-2-*N*-BOC-amino-*N*-[2-(4-methoxyphenyl)ethyl]-3-phenylpropionamide (398 mg, 1 mmol) and trifluoroacetic acid (1.14 g, 10 mmol) in anhydrous DCM (2 mL) was stirred at room temperature for 1 h. After removal of the solvent, the residue was partitioned between ethyl acetate and saturated $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to give **6d** as a pale yellow oil (268 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (t, 2H, J = 7.5 Hz), 7.25−7.19 (m, 3H), 7.06 (d, 2H, J = 8.0 Hz), 6.83 (d, 2H, J = 9.0 Hz), 3.79 (s, 3H), 3.61 (dd, 1H, J = 4.5, 8.5 Hz), 3.53−3.41 (m, 2H), 3.24 (dd, 1H, J = 4.5, 13.5 Hz), 2.73 (t, 2H, J = 8.5 Hz), 2.70 (dd, 1H, J = 9.5, 13.5 Hz). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 174.3, 158.4, 138.2, 131.2, 129.9, 129.5, 128.9, 127.0, 114.2, 56.7, 55.5, 41.3, 40.6, 35.1. $[\alpha]^{24.6}_D$ = +1.2 (*c* 0.5, MeOH). HRESMS [M + H]$^+$: 299.1755 (calcd for [$C_{18}H_{22}N_2O_2$ + H]$^+$, 299.1759).

(*R*)-2-Amino-*N*-benzyl-3-(*tert*-butyldimethylsilanylloxy)propionamide (6f). To a solution of d-serine methyl ester (1.19 g, 10 mmol) in DCM (40 mL) at 0 °C was added *tert*-butyldimethylsilyl chloride (3.16 g, 21 mmol) followed by imidazole (slowly). The mixture was allowed to warm to room temperature and stirred overnight. It was then poured into water (20 mL). The aqueous layer was washed with DCM (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to give (*R*)-2-amino-3-(*tert*-butyldimethylsilanylloxy)propionic acid methyl ester. This material was used without further purification and converted to **6f** followed the general procedure outlined for the preparation of α-amino amides **4** and **6a**−**c**,**e**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (brs,1H), 7.35−7.24 (m, 5H), 4.48 (dd, 1H, J = 6.0, 14.5 Hz), 4.42 (dd, 1H, J = 5.5, 14.5 Hz), 3.87 (dd, 1H, J = 6.0, 10.0 Hz), 3.82 (dd, 1H, J = 4.0, 10.0 Hz), 3.49 (t, 1H, J = 5.5 Hz), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 173.0, 138.6, 128.8, 127.9, 127.6, 65.5, 56.8, 43.4, 26.0, 18.4, −5.2. $[\alpha]^{24.6}_D$ = −4.0 (*c* 0.5, MeOH). HRESMS [M + H]$^+$: 309.1992 (calcd for [$C_{16}H_{28}N_2O_2Si$ + H]$^+$, 309.1998).

General Procedure for the Preparation of Hydantoins 7 from Amino Amides 6. A solution of **6** (0.3 mmol) and pyridine (0.4 mL) in 3 mL of anhydrous DCM under an Ar atmosphere was cooled to 0 °C. A solution of triphosgene (36 mg, 0.12 mmol) in DCM (2 mL) was added. The resulting mixture was stirred at 0 °C for 1.5 h and then at 40 °C for 12 h. The reaction mixture was allowed to cool to room temperature, DCM (10 mL) and 1 N HCl (3 mL) were added. The aqueous layer was washed with DCM (10 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel using DCM/ethyl acetate (80:20) to afford the hydantoins **7**.

(*S*)-5-Benzyl-3-methylimidazolidine-2,4-dione (5).[15a] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.29 (m, 3H), 7.20 (d, 2H, J = 6.8 Hz), 5.18 (brs, 1H), 4.23 (ddd, 1H, J = 1.2, 3.6, 10.0 Hz), 3.33 (dd, 1H, J = 3.6, 14.0 Hz), 2.99 (s, 3H), 2.79 (dd, 1H, J = 10.0, 14.0 Hz). $[\alpha]^{22.3}_D$ = −86.5 (*c* 1.0, acetone) [lit.[15a] $[\alpha]^{24}_D$ = −113.0 (*c* 1.0, acetone)].

(*S*)-5-Benzyl-3-ethylimidazolidine-2,4-dione (7a).[15b] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35−7.28 (m, 3H), 7.20 (d, 2H, J = 7.0 Hz), 5.12 (brs, 1H), 4.22 (ddd, 1H, J = 1.5, 4.0, 9.0 Hz), 3.51 (m, 2H), 3.28 (dd, 1H, J = 4.0, 14.0 Hz), 2.79 (dd, 1H, J = 10.0, 14.0 Hz), 1.11 (t, 3H, J = 7.5 Hz). $[\alpha]^{24.5}_D$ = −92.4 (*c* 0.5, MeOH).

(*S*)-5-Benzyl-3-butylimidazolidine-2,4-dione (7b). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35−7.18 (m, 5H), 5.15 (brs, 1H), 4.22 (ddd, 1H, J = 1.0, 4.0, 9.0 Hz), 3.43−3.36 (m, 2H), 3.27 (dd, 1H, J = 4.0, 14.5 Hz), 2.84 (dd, 1H, J = 9.0, 14.5 Hz), 1.52−1.45 (m, 2H), 1.28−1.18 (m, 2H), 0.89 (t, 3H, J = 7.5 Hz). ^{13}C NMR (100.5 MHz, $CDCl_3$): 173.3, 157.3, 135.4, 129.5, 129.1, 127.7, 58.4, 38.6, 38.2, 30.2, 20.1, 13.8. Mp: 136−137 °C. $[\alpha]^{24.2}_D$ = −86.0 (*c* 0.5, MeOH). FT-IR (KBr pellet, ν_{max}, cm^{-1}): 3315brs, 2952s, 2868m, 1753s, 1708s, 1693s, 1456s, 1426s, 1186m, 1096m, 759m, 707s, 616m. HRESMS [M + H]$^+$: 247.1449 (calcd for [$C_{14}H_{18}N_2O_2$ + H]$^+$, 247.1446).

(*S*)-5-Benzyl-3-benzylimidazolidine-2,4-dione (7c).[15c] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31−7.26 (m, 8H), 7.17−7.15 (m, 2H), 5.32 (brs, 1H), 4.63 (d, 1H, J = 14.5 Hz), 4.58 (d, 1H, J = 14.5 Hz), 4.25 (ddd, 1H, J = 1.5, 4.0, 9.0 Hz), 3.27 (dd, 1H, J = 4.0, 14.0 Hz), 2.79 (dd, 1H, J = 9.0, 14.0 Hz). $[\alpha]^{24.5}_D$ = −62.8 (*c* 0.5, MeOH).

(*R*)-5-Benzyl-3-[2-(4-methoxyphenyl)ethyl]imidazolidine-2,4-dione (7d). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (t, 2H, J = 8.0 Hz), 7.27 (t, 1H, J = 8.0 Hz), 7.18 (d, 2H, J = 7.0 Hz), 7.12 (d, 2H, J = 7.0 Hz), 6.83 (d, 2H, J = 8.0 Hz), 5.08 (brs, 1H), 4.15 (ddd, 1H, J = 1.0, 2.5, 7.5 Hz), 3.78 (s, 3H), 3.69 (ddd, 1H, J = 6.5, 8.5, 13.5 Hz), 3.65 (ddd, 1H, J = 6.5, 8.5, 14.0 Hz), 3.23 (dd, 1H, J = 4.0, 9.0 Hz), 2.79 (ddd, 2H, J = 2.5, 5.2, 8.0 Hz), 2.68 (dd, 1H, J = 9.5, 14.0 Hz). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 173.0, 158.6, 156.9, 135.6, 130.1, 130.0, 129.4, 129.2, 127.7, 114.2, 58.4, 55.5, 40.1, 38.3, 33.1. Mp: 149−150 °C. $[\alpha]^{24.6}_D$ = +122.4 (*c* 0.5, MeOH). FT-IR (KBr pellet, ν_{max}, cm^{-1}): 3288brs, 2936m, 2837m, 1755s, 1705s, 1696s, 1513s, 1461s, 1241s, 1176m, 1033m, 753m, 703m, 628m. HRESMS [M + H]$^+$: 325.1561 (calcd for [$C_{19}H_{20}N_2O_3$ + H]$^+$, 325.1552).

(*S*)-3-Benzyl-5-isobutylimidazolidine-2,4-dione (7e). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41−7.25 (m, 5H), 5.35 (s, 1H), 4.68 (d, 1H, J = 18.5 Hz), 4.63 (d, 1H, J = 18.5 Hz), 4.04 (dd, 1H, J = 3.0, 12.5 Hz), 1.85−1.70 (m, 2H), 1.59−1.47 (m, 1H), 0.96 (d, 3H, J = 3.0 Hz), 0.95 (d, 3H, J = 2.5 Hz). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 174.3, 157.3, 136.2, 128.9, 128.8, 128.1, 56.1, 42.4, 41.1, 25.5, 23.2, 21.8. Mp: 79−80 °C. $[\alpha]^{24.2}_D$ = −55.2 (*c* 0.5, MeOH). FT-IR (KBr pellet, ν_{max}, cm^{-1}): 3238brs, 2959s, 2875m, 1767s, 1712s, 1450s, 1350s, 1198m, 1079m, 748m, 692s, 630m; HRESMS [M + H]$^+$: 247.1451 (calcd for [$C_{14}H_{18}N_2O_2$ + H]$^+$, 247.1446).

(*R*)-3-Benzyl-5-(*tert*-butyldimethylsilanyloxymethyl)imidazolidine-2,4-dione (7f). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, 2H, J = 6.5 Hz), 7.31 (t, 2H, J = 6.5 Hz), 7.27 (d, 1H, J = 7.0 Hz), 5.31 (brs, 1H), 4.66 (d, 1H, J = 14.5 Hz), 4.63 (d, 1H, J = 14.5 Hz), 4.10 (dd, 1H, J = 3.5, 6.0 Hz), 3.92 (dd, 1H, J = 3.5, 11.0 Hz), 3.84 (dd, 1H, J = 6.0, 11.0 Hz), 0.83 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 171.7, 157.6, 136.1, 128.9, 128.8, 128.1, 62.7, 59.7, 42.4, 25.9, 18.4, −5.31, −5.34. Mp: 128−129 °C. $[\alpha]^{24.0}_D$ = +58.8 (*c* 0.5, MeOH). FT-IR (KBr pellet, ν_{max}, cm^{-1}): 3333brs, 2954s, 2928s, 2856s, 1764s, 1707s, 1449s, 1425s, 1126s, 984m, 777s, 714m, 624m. HRESMS [M + H]$^+$: 335.1796 (calcd for [$C_{17}H_{26}N_2O_3Si$ + H]$^+$, 335.1791).

[2*S*(4*S*)]-2-(4-Benzyl-2,5-dioxoimidazolidin-1-yl)-3-phenylpropionic Acid Methyl Ester (7g). To *N*-Boc-L-phenylalanyl-L-phenylalanine methyl ester[19] (85 mg, 0.2 mmol) in methanol (1 mL) at 0 °C was added acetyl chloride (0.4 mL) under argon. The mixture was stirred at room temperature for 2 h. Concentration of the mixture gave a white solid (HCl salt), which was used without further purification following the general procedure for converting **6** to **7**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.25 (m, 5H), 7.21−7.24 (m, 3H), 7.11−7.10 (m, 2H), 5.05 (s, 1H), 4.98 (dd, 1H, J = 10.5, 6.5 Hz), 4.06 (ddd, 1H, J = 11.0, 3.5, 1.0 Hz), 3.80 (s, 3H), 3.48−3.50 (m, 2H), 3.07 (dd, 1H, J = 13.5, 3.5 Hz), 2.12 (dd, 1H, J = 13.5, 11.0 Hz). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 172.5, 169.2, 155.8, 136.7, 135.9, 129.4, 129.3, 129.2, 128.8, 127.7, 127.3, 58.4, 53.4, 53.1, 38.4, 34.3. Mp: 184−185 °C. $[\alpha]^{21.4}_D$ = −207.8 (*c* 1.0, acetone). FT-IR (KBr pellet, ν_{max}, cm^{-1}): 3296brs, 3029m, 2924m, 1761s, 1710s, 1426s, 1361s, 1246s, 1048m, 763m, 720m, 582m. Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.07; H, 5.26; N, 7.95.

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Supporting Information Available: ^{1}H and/or ^{13}C NMR spectra for **4**, **5**, **6a**−**f**, and **7a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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