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Enantiomerically Pure Synthesis of β-Substituted γ-Butyrolactones: A Key Intermediate to Concise Synthesis of Pregabalin

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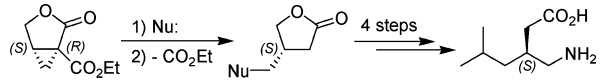

Chiral β-substituted γ-butyrolactones are known to be important intermediates for many biologically active compounds such as γ-aminobutyric acid (GABA) derivatives and lignans. We have developed a general, convenient, and scalable synthetic method for enantiomerically pure β-substituted γ-butyrolactones, with either configuration, via nucleophilic cyclopropane ring opening of (1*S*,5*R*)- or (1*R*,5*S*)-bicyclic lactone followed by decarbethoxylation. The utility of our method was demonstrated by streamlined synthesis of pregabalin ((*S*)-3-isobutyl-γ-aminobutyric acid), an anticonvulsant drug for the treatment of peripheral neuropathic pain.

Chiral γ-butyrolactones with various aromatic or aliphatic substituents at the β-stereocenter are found in a number of biologically active natural products (lignans) such as (−)-enterolactone, (−)-matairesinol, and (−)-arctigenin.[1] They also can be key precursors to β-substituted γ-amino acids. Traditionally, development of efficient synthetic protocols for GABA (γ-aminobutyric acid) derivatives, including pregabalin, has been a topic of keen interest for synthetic, bioorganic, and medicinal chemists because of the therapeutic potential of such compounds.[2] Recent advances in foldamer research have stimulated additional interest in γ-amino acids.[3,4a] Efficient synthetic methodologies for various types of γ-amino acids are essential for the systematic conformational studies of γ-peptide foldamers because the substitution pattern of side chains on the γ-amino acid skeleton is known to be a determinant of the conformation.[4] The conformational propensity of γ^3-amino acid residues has not yet been explored because the few examples reported to date have displayed insufficient NMR signal dispersion.[4e] This problem could potentially be overcome by incorporation of more diverse side chains onto the backbone. In this context, we became interested in developing general and efficient synthetic methodology for protected γ^3-amino acids with diverse side chain functionality (Figure 1).

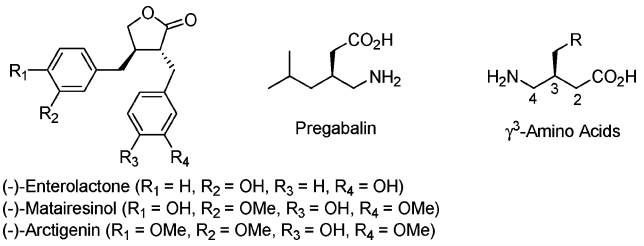

FIGURE 1. Biologically active compounds from β-substituted γ-butyrolactone.

Many chiral β-substituted γ-butyrolactone syntheses have been reported in the past. The strategies that have led to this skeleton include catalytic asymmetric Baeyer−Villiger reaction,[5] asymmetric C−H insertion reaction,[6] asymmetric hydrogenation,[7] chiral auxiliary-based synthesis,[8] synthesis from natural chiral pool building blocks,[9] and enzymatic resolution.[10] We envisioned that chiral β-substituted γ-butyrolactones would be

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(1) For a recent review on the synthesis of lignans, see: Sefkow, M. *Top. Curr. Chem.* **2005**, *243*, 185.

(2) (a) For review on 3-substituted GABA analogues with CNS activity, see: Bryans, J. S.; Wustrow, D. J. *Med. Res. Rev.* **1999**, *19*, 149. (b) Dworkin, R. H.; Kirkpatrick, P. *Nat. Rev. Drug Discovery* **2005**, *4*, 455. (c) Belliotti, T. R.; Capiris, T.; Ekhato, I. V.; Kinsora, J. J.; Field, M. J.; Heffner, T. G.; Meltzer, L. T.; Schwarz, J. B.; Taylor, C. P.; Thorpe, A. J.; Vartanian, M. G.; Wise, L. D.; Zhi-Su, T.; Weber, M. L.; Wustrow, D. J. *J. Med. Chem.* **2005**, *48*, 2294. (d) Yuen, P.; Kanter, G. D.; Taylor, C. P.; Vartanian, M. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 823.

(3) (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (b) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodiversity* **2004**, *1*, 1111 and references therein. (c) Hill, D. J.; Mio, M. J.; Prince, R. B.: Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893. (d) Sharma, G. V. M.; Jadhav, V. B.; Ramakrishna, K. V. S.; Jayaprakash, P.; Narsimulu, Subash, K., V.; Kunwar, A. C. *J. Am. Chem. Soc.* **2006**, *128*, 14657.

(4) (a) Hanessian, S.; Luo, X.; Schaum, R.; Michnick, S. *J. Am. Chem. Soc.* **1998**, *120*, 8569. (b) Hintermann, T.; Gademann, K.; Jaun, B.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 983. (c) Woll, M. G.; Lai, J. R.; Guzei, I. A.; Taylor, S. J. C.; Smith, M. E. B.; Gellman, S. H. *J. Am. Chem. Soc.* **2001**, *123*, 11077−11078. (d) Seebach, D.; Hook, D. F.; Glattli, A. *Biopolymers (Pept. Sci.)* **2006**, *84*, 23. (e) Seebach, D.; Brenner, M.; Rueping, M.; Jaun, B. *Chem. Eur. J.* **2002**, *8*, 573.

(5) (a) Frison, J.; Palazzi, C.; Bolm, C. *Tetrahedron* **2006**, *62*, 6700. (b) Bolm, C.; Beckmann, O.; Cosp, A.; Palazzi, C. *Synlett* **2001**, 1461. (c) Bolm, C.; Beckmann, O.; Palazzi, C. *Can. J. Chem.* **2001**, *79*, 1593.

(6) Bode, J. W.; Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L. *J. Org. Chem.* **1996**, *61*, 9146.

(7) (a) Kamlage, S.; Sefkow, M; Pool-Zobel, B. L.; Peter, M. G. *Chem. Commun.* **2001**, 331. (b) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253. (c) Kamlage, S.; Sefkow, M.; Zimmermann, N.; Peter, M. G. *Synlett* **2002**, 77. (d) Morimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron* **1993**, *49*, 1793.

(8) (a) Koch, S.; Chamberlin, A. *J. Org. Chem.* **1993**, *58*, 2725. (b) Sibi, M. P.; Liu Johnson, P., M. D. *Can. J. Chem.* **2000**, *78*, 133. (c) de L Vanderlei, J. M.; Coelho, F.; Almeida, W. P. *Synth. Commun.* **1998**, *28*, 3047.

(9) (a) Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1979**, 3315. (b) Camps, P.; Font, J.; Ponsati, O. *Tetrahedron Lett.* **1981**, *22*, 1471. (c) Yoda, H.; Naito, S.; Takabe, K.; Tanaka, N.; Hosoya, K. *Tetrahedron Lett.* **1990**, *31*, 7623.

(10) (a) Caro, Y.; Masaguer, C. F.; Raviña, E. *Tetrahedron: Aymmetry* **2001**, *12*, 1723. (b) Brinksma, J.; van der Deen, H.; van Oeveren, A.; Feringa, B. L. *J. Chem. Soc., Perkin Trans.* **1998**, *1*, 4159. (c) Barnier, J. P.; Blanco, L.; Guibé-Jampel, E.; Rousseau, G. *Tetrahedron* **1989**, *45*, 5051.

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SCHEME 1. Synthetic Strategy for Chiral β-Substituted γ-Butyrolactone via Chiral Bicyclic Lactone

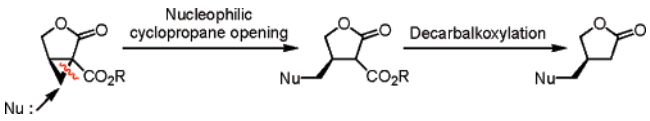
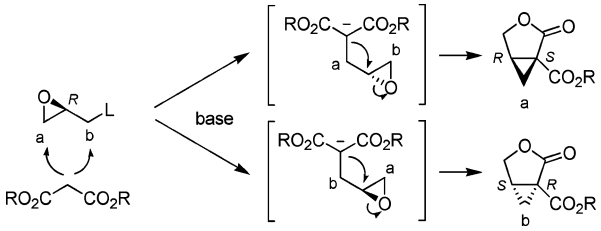


TABLE 1. Preparation of Chiral Bicyclic Lactones



leaving group (L)	R	% ee	yield (%)	ref
OTf[a]	*t*-Bu	91	48	15a
Cl[b]	Me	93.4	36	12a
Cl[c]	Et	>97	65	16
Cl[d]	Et	>99[e]	59[e]	

[a] 92% ee. [b] 97% ee. [c] >98% ee. [d] >99% ee. [e] Our results.

easily prepared by nucleophilic opening of the cyclopropane ring[11] of enantiomerically pure chiral [3.1.0]bicyclic lactone followed by decarbethoxylation (Scheme 1).

This type of bicyclic lactone has been often used as a precursor for preparation of cyclopropane derivatives by opening of the γ-lactone ring,[12] but examples of cyclopropane ring opening from this particular bicyclic lactone to generate γ-lactone derivatives are rare. Hamilton's group[13] and Chavan's group[14] have reported cyclopropane ring-opening reactions with sulfur and oxygen nucleophiles, respectively, but no further examples are known.

The desired chiral bicyclic lactone can be easily prepared in one pot from chiral epichlorohydrin by intramolecular double displacement of alkyl malonate anion followed by lactonization.[12a] It is reported that initial nucleophillic attack occurs exclusively at the a-carbon center followed by Payne rearrangement to form the epoxide intermediate when the leaving group is chloride, whereas b-carbon attack is favored to generate the intermediate directly when triflate is the leaving group (Table 1).[15]

The availability of enantiomerically pure bicyclic lactone is crucial in generating β-substituted γ-butyrolactones with high enantiomeric purity. We prepared (1*S*,5*R*)-bicyclic lactone from (*R*)-epichlorohydrin (>99% ee) and diethyl malonate in a manner described by Tsuji and co-workers.[16] Previously, the bicyclic lactone was purified by silica gel column chromatography, but this approach is not practical for multigram scale synthesis. Fortunately, we have found that the bicyclic lactone

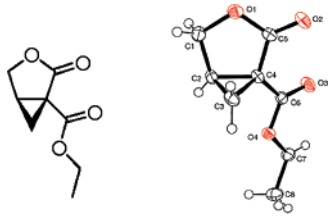
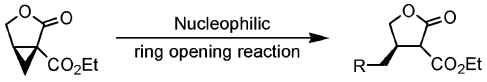
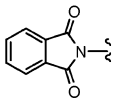


FIGURE 2. Crystal structure of (1*S*,5*R*)-bicyclic lactone: (a) Bond lengths (Å): C(2)−C(3), 1.476(2); C(3)−C(4), 1.533(2); C(2)−C(4), 1.520(2). (b) Angles (deg): C(5)−C(4)−C(3), 112.21(15); C(6)−C(4)−C(2), 124.14(14).

TABLE 2. Reaction Scope of Nucleophilic Cyclopropane Ring-Opening Reaction



Entry	R	Yield (%)	Reaction Conditions
1		95	*i*-PrMgCl, CuI, THF, -45~-15°C
2		94	*c*HxMgCl, CuI, THF, -45~-15°C
3		78	PhMgBr, CuBr-Me_2S, THF/Me_2S, rt
4		46	VinylMgBr, CuBr-Me_2S, THF/Me_2S, rt
5		66	K-Phthalimide, 18-Crown-6, DMF, 70°C
6		68 43	NaN_3, AcOH, Et_3N, DMF, 70°C NaN_3, DMSO/EtOH (1:1), 55°C

could be easily purified by vacuum distillation. We also have succeeded in crystallizing the bicyclic lactone for the first time by simply keeping the distilled compound at −20 °C overnight to obtain needle-like crystal (Figure 2).

We obtained the desired bicyclic lactone in 59% yield with >99% ee via our modified protocol. The enantiomeric purity is improved relative to earlier reports (Table 1; see the Supporting Information). The improved ee value is presumably due to the higher ee of the starting chiral epichlorohydrin and the exclusive initial nucleophilic attack at the a-carbon center. After extensive experimentation, we found that the crystallization is possible only when the bicyclic lactone is exceptionally pure. The opposite enantiomeric (1*R*,5*S*)-bicyclic latone was synthesized from (*S*)-epichlorohydrin in identical yield and enantiomeric purity.

With the enantiomerically pure bicyclic lactone in hand, we investigated the scope of the nucleophilic cyclopropane ring-opening reaction for various types of nucleophiles (Table 2). For the addition of carbon nucleophiles, we used in situ generated cuprates from the corresponding Grignard reagents and copper sources (CuI for sp^3 carbon nucleophiles and CuBr−SMe_2 for sp^2 carbon nucleophiles). The reaction worked very well with sp^3 and sp^2 carbon nucleophiles. Addition of isopropyl and cyclohexyl cuprates at −45 °C for 30 min gave the corresponding lactones as 9:1 to 18:1 diastereomeric mixtures

(11) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.
(12) (a) Pirrung, M. C.; Dunlap, S. E.; Trinnks, U. P. *Helv. Chim. Acta* **1989**, *72*, 1301. (b) Džolic, Z.; Krištafor, V.; Cetina, M.; Nagl, A.; Hergold-Brundi, A.; Mrvoš-Sermek, D.; Burgemeiser, T.; Grdiša, M.; Slade, N.; Pavelic, K.; Balzarini, J.; Clercq, E.; Mintas, M. *Nucleosides, Nucleotides Nucleic Acids* **2003**, *22*, 373. (c) Finta, Z.; Hell, Z.; Cwik, A.; Toke, L. *J. Chem. Res. Synop*. **2002**, *9*, 459. (d) Burgess, K.; Ke, C. *Synthesis* **1996**, *12*, 1463. (e) Burgess, K.; Lim, D. Y. *Tetrahedron Lett.* **1995**, *36*, 7815.
(13) Lee, C.; Lee, K.; Hamilton, A. *Tetrahedron Lett.* **2001**, *42*, 211.
(14) Chavan, S.; Pasupaphy, K.; Shivasankar, K. *Synth. Commun.* **2004**, *34*, 397.
(15) (a) Burgess, K.; Ho, K.-K. *J. Org. Chem.* **1992**, *57*, 5931. (b) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589.
(16) Sekiyama, T.; Hatsuya, S.; Tanaka, Y.; Uchiyama, M.; Ono, N.; Iwayama, S.; Oikawa, M.; Suzuki, K.; Okunishi, M.; Tsuji, T. *J. Med. Chem.* **1998**, *41*, 1284.

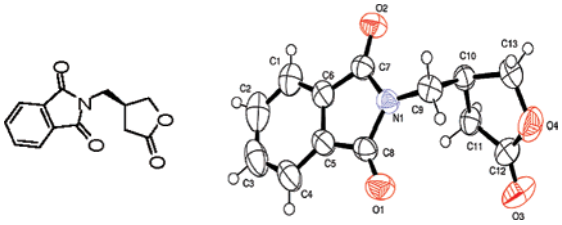


FIGURE 3. Crystal structure of β-phthalimidylmethyl γ-butyrolactone.

in excellent yield (95% and 94%, respectively; entries 1 and 2). The phenyl-substituted lactone was generated at room temperature in good yield (78%; entry 3), which is interesting because β-substituted γ-butyrolactones possessing aromatic substitutents are key intermediates for streamlined synthesis of various lignans. The yield was not satisfactory for vinyl cuprate (46%) because of the formation of unidentified side products (entry 4). Addition of nitrogen nucleophiles, such as phthalimidate and azide anions, were successfully achieved with moderate yields (66% and 68%, respectively), but these reactions required elevated temperature (70 °C; entries 5 and 6). In the case of azide, an improved yield was obtained when an acidic additive was present.[17] The structures of the products were analyzed by NMR spectroscopy (see the Supporting Information), and the regioselective nucleophilic addition at C3[18] was confirmed by obtaining a crystal structure of the γ-butyrolactone with a phthalimidyl substituent (Figure 3).[19] After addition of the nucleophile, the resulting diastreomeric mixture of lactones was subjected to decarbethoxylation by heating with lithium chloride in DMSO in the presence of water[20] to generate the corresponding β-substituted γ-butyrolactones in high yield (79%).

To demonstrate the synthetic value of our methodology, it was applied to the synthesis of pregabalin (**5**; (*S*)-3-isobutyl-γ-aminobutyric acid), an anticonvulsant drug for neuropathic pain treatment.[21] Pregabalin could be easily synthesized in a straightforward manner from (1*R*,5*S*)-bicyclic lactone **1** (Scheme 2). Nucleophilic addition of isopropyl cuprate to **1** followed by decarbethoxylation gave (*S*)-3-isobutyl-γ-butyrolactone **2** in 75% overall yield. The lactone ring was easily opened by TMS-Br and ethanol to give bromide **3** in 90% yield. Azide substitution, saponification, and subsequent hydrogenation provided pregabalin (**5**) in 85% overall yield.

Although there is no chance of epimerization at the stereocenter in our synthetic route, we determined the enantiomeric purity of intermediate **4**, which was transformed into the corresponding trifluoroacetamide by hydrogenation in the presence of trifluoroacetic anhydride. Chiral GC analysis revealed

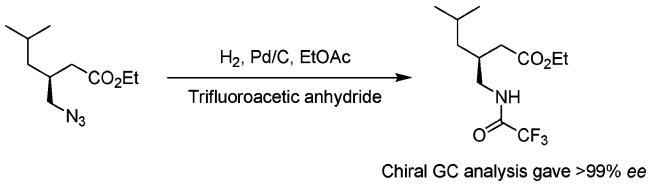
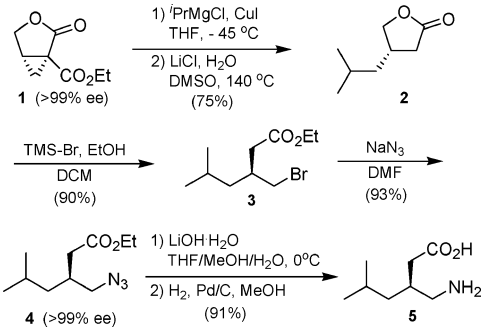


FIGURE 4. Enantiomeric purity of compound **4**.

SCHEME 2. Streamlined Synthesis of Pregabalin



that the optical purity of **4** was >99% ee (see the Supporting Information), which confirmed that the enantiomeric purity of the starting bicyclic lactone was retained during the synthesis (Figure 4). Thus, we could obtain pregabalin in six steps and 57% overall yield from (1*R*,5*S*)-bicyclic lactone in very high enantiomeric purity (>99% ee).

In summary, we have developed a general, convenient, and scalable synthetic method for enantiomerically pure β-substituted γ-butyrolactones, in either enantiomeric series, by nucleophilic cyclopropane ring opening of (1*S*,5*R*)- or (1*R*,5*S*)-bicyclic lactone followed by decarbethoxylation. We have demonstrated the utility of our methodology by developing a concise synthetic route to pregabalin. Our method offers access to γ^3-amino acids with diverse types of substituents and provides a new way to achieve concise syntheses of many biologically active molecular targets via β-substituted γ-butyrolactones as key intermediates.

Experimental Section

Modified Synthetic Protocol for (1*S*,5*R*)- and (1*R*,5*S*)-[3.1.0]-Bicyclic Lactones (1*S*,5*R*)-[3.1.0]Bicyclic Lactone (*ent*-1). Sodium (3.09 g, 134.4 mmol) was dissolved in anhydrous ethanol (250 mL) for 30 min. The solution was cooled to 0 °C, and then diethylmalonate (21.4 mL, 141.0 mmol) was added dropwise. After the solution was warmed to room temperature, (*R*)-epichlorohydrin (10 mL, 127.9 mmol) was added slowly by syringe pump. After the addition, the reaction mixture was heated to 75 °C for 36 h. Distilled water was carefully added until the solution went clear. Ethanol was removed under reduced pressure. The aqueous layer was extracted with methylene chloride (×3) and was dried over anhydrous magnesium sulfate. The residue was concentrated under reduced pressure. The resulting oil was purified via vacuum distillation (1.5 mmHg). After removal of excess diethyl malonate (at 42−43 °C), the product was obtained at 110−112 °C as a colorless oil, which was then solidified by keeping at −20 °C to give a needle-like crystal (12.23 g, 59% yield, >99% ee). The enantiomeric excess was determined by chiral GC analysis using a CHIRALDEX β-DM column (130 °C, 1.4 kgf/cm^3). The (1*S*,5*R*)-isomer had a retention time of 14.76 min: mp = 38−40 °C; $[\alpha]^{20}_D$ = −166.91 (*c* 1.22, EtOH), $[\alpha]^{25}_D$ = −135.41 (*c* 1.00, CH_2Cl_2) (lit.[16] $[\alpha]^{25}_D$ = −146.58 (*c* 1.22, EtOH) for >97% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (1H, dd, J = 4.73, 9.42 Hz), 4.23 (2H, q, J = 7.14 Hz), 4.16 (1H, d, J = 9.43 Hz), 2.70 (1H, m), 2.05

(17) Guerin, D. J.; Horstmann, T. E.; Miller, S. J. *Org. Lett.* **1999**, *1*, 1107.
(18) The atom number is illustrated for the crystal structure (Figure 2).
(19) The melting point of the crystal is 79−81 °C.
(20) Yan, B.; Spilling, C. D. *J. Org. Chem.* **2004**, *69*, 2859.
(21) For recent enantioselective synthesis of pregabalin, see: (a) Hoge, G. *J. Am. Chem. Soc.* **2003**, *125*, 10219. (b) Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442. (c) Mita, T.; Sasaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 514. (d) Hoekstra, M. S.; Sobieray, D. M.; Schwindt, M. A.; Mulhern, T. A.; Grote, T. M.; Huckabee, B. K.; Hendrickson, V. S.; Franklin, L. C.; Granger, E. J.; Karrick, G. L. *Org. Process Rev. Dev.* **1997**, *1*, 26 and ref 2d. (e) Chen, Z.; Chen, Z.; Jiang, Y.; Hu, W. *Synlett* **2004**, *10*, 1763. (f) Rodriguez, V.; Quintero, L.; Sartillo-Piscil, F. *Tetrahedron Lett.* **2007**, *48*, 4305. (g) Burk, M. J.; de Koning, P. D.; Grote, T. M.; Hoekstra, M. S.; Hoge, G.; Jennings, R. A.; Kissel, W. S.; Le, T. V.; Lennon, I. C.; Mulhern, T. A.; Ramsden, J. A.; Wade, R. A. *J. Org. Chem.* **2003**, *68*, 5731.

(1H, dd, J = 4.77, 7.98 Hz), 1.35 (1H, t, J = 5.14 Hz), 1.28 (3H, t, J = 7.13 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 166.7, 67.0, 62.0, 29.3, 27.9, 20.7, 14.1; HRMS (EI) calcd for $C_8H_{10}O_4$ 170.0579, found 170.0571.

(1*R*,5*S*)-[3.1.0]Bicyclic Lactone (1). (1*R*,5*S*)-Isomer was synthesized from (*S*)-epichlorohydrin in an identical yield and enantiomeric purity (59%, >99% ee) and had a retention time of 16.88 min in a chiral GC analysis: $[\alpha]^{20}_D$ = +166.39 (*c* 1.22, EtOH), $[\alpha]^{25}_D$ = +134.81 (*c* 1.00, CH_2Cl_2) (lit.[16] $[\alpha]^{25}_D$ = +145.48 (*c* 1.22, EtOH) for >97% ee).

Representative Nucleophilic Cyclopropane Ring-Opening Reaction (Table 2). (4*R*)-Ethyl 4-Benzyl-2-oxotetrahydrofuran-3-carboxylate. To a stirred solution of CuBr−Me_2S (362 mg, 1.76 mmol) in anhydrous THF (3.5 mL) and Me_2S (1.0 mL) was added phenylmagnesium bromide in THF (1.0 M, 3.53 mL, 3.53 mmol) at −40 °C. The solution was stirred for 20 min, with warming to −20 °C. (1*S*,5*R*)-Bicyclic lactone (200 mg, 1.18 mmol) in THF (3 mL) was added slowly over 1 h to the reaction mixture via cannula. After 1.5 h of stirring at room temperature, the reaction mixture was quenched with saturated ammonium chloride solution. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (×2). The combined organic layer was washed with 17% aqueous NH_4OH solution and brine and then was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 10% ethyl acetate/hexane to afford (4*R*)-ethyl 4-benzyl-2-oxotetrahydrofuran-3-carboxylate (224.3 mg, 77.6%) as a colorless oil: ^{1}H NMR of the major isomer (400 MHz, $CDCl_3$) δ 7.29 (2H, t, J = 7.26 Hz), 7.22 (1H, t, J = 8.11 Hz), 7.13 (2H, d, J = 8.33 Hz), 4.40 (1H, t, J = 8.05 Hz), 4.08 (2H, m), 3.97 (1H, t, J = 8.57 Hz), 3.28 (2H, m), 2.80 (2H, d, J = 6.38 Hz), 1.20 (3H, t, J = 7.17 Hz); ^{13}C NMR of the major isomer (100 MHz, $CDCl_3$) δ 171.8, 167.2, 137.0, 128.78, 128.76, 127.0, 71.3, 62.1, 52.00, 4165, 37.8, 13.9; HRMS (EI) calcd for $C_{14}H_{16}O_4$ 248.1049, found 248.1048.

Synthesis of Pregabalin (Scheme 2). (*S*)-4-Isobutyldihydrofuran-2-one (2). To a stirred suspension of CuI (0.63 g, 3.31 mmol) in anhydrous THF (20 mL) at −45 °C was added isopropylmagnesium chloride in THF (2.0 M, 8.23 mL, 16.46 mmol) dropwise. The organocuprate formation was typically complete within 1 h. (1*R*,5*S*)-Bicyclic lactone **1** (1.12 g, 6.58 mmol) in anhydrous THF (20 mL) was added to the solution via cannula at −45 °C. The resulting solution was stirred for 30 min with warming to −15 °C, which was quenched with saturated ammonium chloride solution, then stirred overnight with diethyl ether at room temperature. The ethereal layer was separated, and the aqueous layer was extracted with ethyl acetate (×2). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 10% ethyl acetate/hexane to afford an 8:1 diastereomeric mixture of lactones (1.34 g, 95% yield): ^{1}H NMR of the crude product (400 MHz, $CDCl_3$) δ 4.49 (1H, dd, J = 8.80, 7.82 Hz), 4.23 (2H, q, J = 7.11 Hz), 3.85 (1H, t, J = 8.68 Hz), 3.18 (1H, d, J = 9.39 Hz), 3.03 (1H, m), 1.53 (1H, m), 1.42 (1H, m), 1.38 (1H, m), 1.31 (3H, t, J = 8.96 Hz), 0.90 (6H, t, J = 6.62 Hz); ^{13}C NMR of the crude product (100 MHz, $CDCl_3$) δ 172.1, 167.8, 72.2, 62.1, 52.9, 41.7, 38.3, 26.0, 22.6, 22.4, 14.1; HRMS (EI) calcd for $C_{11}H_{18}O_4$ 214.1205, found 214.1208.

The diastereomeric mixture of lactones (991 mg, 4.63 mmol) and LiCl (392 mg, 9.25 mmol) in DMSO/H_2O (50 mL/1 mL) was heated for 18 h at 140 °C. After the reaction was complete, water (50 mL) was added to the solution at room temperature. The solution was extracted with ethyl acetate (×3), and the combined organic layer was washed sequentially with 1 N HCl solution, saturated $NaHCO_3$ solution, and brine. The solution was dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residue was purified by silica gel column chromatography using 10% ethyl acetate/hexane to afford **2** (520 mg, 79.1%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (1H, t, J = 8.53 Hz), 3.86 (1H, t, J = 8.74 Hz), 2.60 (2H, m), 2.13 (1H, m), 1.55 (1H, m), 1.34 (2H, t, J = 6.95 Hz), 0.89 (6H, t, J = 6.21 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 73.5, 42.2, 34.8, 33.8, 26.3, 22.6, 22.4; HRMS (EI) calcd for $C_8H_{14}O_2$ 142.0994, found 142.0990.

With the (*S*)-β-isobutyl γ-butyrolactone in hand, **3** and **4** were synthesized by straightforward manner as described in the Supporting Information.

(*S*)-3-Aminomethyl-5-methylhexanoic Acid (Pregabalin) (5). To a stirred solution of **4** (748 mg, 3.51 mmol) in THF/MeOH/H_2O (6/3/1, 30 mL) was added lithium hydroxide monohydrate (736 mg, 17.5 mmol). The reaction mixture was refluxed for 15 min. After the reaction was complete, the organic solvents were removed under reduced pressure. The aqueous layer was acidified with 6 N HCl and then extracted with methylene chloride (×3). The combined organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography using 5% methanol/methylene chloride to afford (*S*)-3-azidomethyl-5-methylhexanoic acid (590.4 mg, 90.9%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (1H, br), 3.39 (1H, dd, J = 12.24, 4.92 Hz), 3.29 (1H, dd, J = 12.24, 6.28 Hz), 2.36 (2H, m), 2.15 (1H, m), 1.60 (1H, m), 1.24 (1H, m), 1.18 (1H, m), 0.89 (6H, dd, J = 6.58, 2.20 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ1 79.1, 54.8, 41.1, 36.7, 33.0, 25.1, 22.6, 22; HRMS (EI) calcd for $C_8H_{15}N_3O_2$ 185.1164, found 185.1167.

A solution of (*S*)-3-azidomethyl-5-methylhexanoic acid (569.7 mg, 3.08 mmol) and 10% Pd/C (90 mg) in MeOH (30 mL) was stirred for 3 h under hydrogen balloon. After completion of the reaction, the reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure to afford 3-aminomethyl-5-methylhexanoic acid (pregabalin) (**5**) (485 mg, 99.0%) as a white solid: mp = 182−183 °C; $[\alpha]^{20}_D$ = +6.0 (*c* 0.54, H_2O); ^{1}H NMR (400 MHz, CD_3OD) δ 2.95 (1H, dd, J = 12.84, 3.54 Hz), 2.82 (1H, dd, J = 12.82, 7.94 Hz), 2.44 (1H, dd, J = 15.73, 3.37 Hz), 2.25 (1H, dd, J = 15.70, 8.76 Hz), 2.06 (1H, m), 1.69 (1H, m), 1.23 (2H, m), 0.92 (6H, t, J = 6.42 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 180.6, 45.9, 43.4, 43.1, 33.2, 26.2, 23.2, 22.6; HRMS (EI) calcd for $C_8H_{17}NO_2$ 159.1259, found 159.1259.

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Supporting Information Available: General experimental procedures, experimental details for the synthesis of compounds in entries 1−6 of Table 2, and **3**, **4** in Scheme 2, copies of ^{1}H and ^{13}C NMR spectra of compounds in Table 2 and Scheme 2, chiral GC analysis data of (1*R*,5*S*)- and (1*S*,5*R*)-bicyclic lactones and the trifluoroacetyl derivative of **4**, and CIF files for (1*S*,5*R*)-bicyclic lactone and β-phthalimidylmethyl γ-butyrolactone. This material is available free of charge via the Internet at http://pubs.acs.org.

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