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One-Step Highly Diastereoselective Synthesis of γ-Aminoalkyl-Substituted γ-Butyrolactones by an Asymmetric Samarium-Mediated Ketyl−Alkene Coupling Reaction

Shin-ichi Fukuzawa,* Manabu Miura, and Takahide Saitoh

Department of Applied Chemistry, Institute of Science and Engineering, Chuo University, 1-13-27 Kasuga, Bunkyo-ku, Tokyo 112-8551, Japan

fukuzawa@chem.chuo-u.ac.jp

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Abstract: The samarium(II) iodide mediated reaction of *N*,*N*-dibenzyl-protected (*S*)-α-amino aldehydes with (1*S*,2*R*)-*N*-methylephedrinyl acrylate gave the (4*R*,1′*S*)-γ-(aminoalkyl)-γ-butyrolactones in good yields with high diastereoselectivities (up to 80% de); (4*R*,1′*S*)-γ-amino-(2-phenylethyl)-γ-butyrolactone (**6a**), which should be a potent precursor for γ-secretase inhibitors, was obtained with high de value.

Hydroxyethylene dipeptide isosteres, i.e., the δ-amino-γ-hydroxy acids **1** (Figure 1), are pharmaceutically important compounds with structures basic for HIV protease inhibitors and γ-secretase inhibitors which are potential curatives for Alzheimers disease, especially when R^1 and R^2 are benzyl (Bn).[1] γ-(Aminoalkyl)-γ-butyrolactones should be useful starting compounds for the preparation of **1** if the α-substituent (R^2) can be introduced stereoselectively.[1b,c] Then, the stereocontrolled syntheses of γ-(aminoalkyl)-γ-butyrolactones have been intensively studied and most of the methods employ chiral amino aldehydes or esters as starting compounds.[2] The allylation of amino aldehydes with allylsilane may be the simplest way, which requires only a few steps to access the γ-(aminoalkyl)-γ-butyrolactones, but the stereoselectivity is not satisfactory in some cases (70% de).[2f] The indium-mediated allylation of amino aldehydes has been recently reported and affords α-methylene-γ-(aminoalkyl)-γ-butyrolactones in good yields, but the problem of unsatisfactory selectivities (30−70% de) remains.[3] Recently, Nadin et al. reported the stereoselective synthesis of (4*R*,1′*S*)-γ-(protected-amino)-γ-butyrolactones via protected α-amino epoxides.[2a] Aguilar et al. reported the synthetic methods of (4*S*,1′*S*)-γ-(protected-amino)-γ-butyrolactones via protected α-amino epoxides, in which the key step is the Sharpless oxidation of allylic alcohols.[2g] These methods seem to be useful for obtaining diastereomerically pure amino lactones but require several steps and their overall yields are not satisfactory (30% from a chiral α-amino ester and 14% from a chiral epoxy alcohol). Thus, the synthetic methods so far reported have the drawback of an unsatisfactory stereoselectivity or multistep procedure. We wish to report here the one-step, highly stereoselective synthesis of (4*R*,1′*S*)-γ-(aminoalkyl)-γ-butyrolactones by the samarium(II) iodide methodology:[4] this method can provide the potent precursor of γ-secretase inhibitors where the alkyl group is 2-phenylethyl.

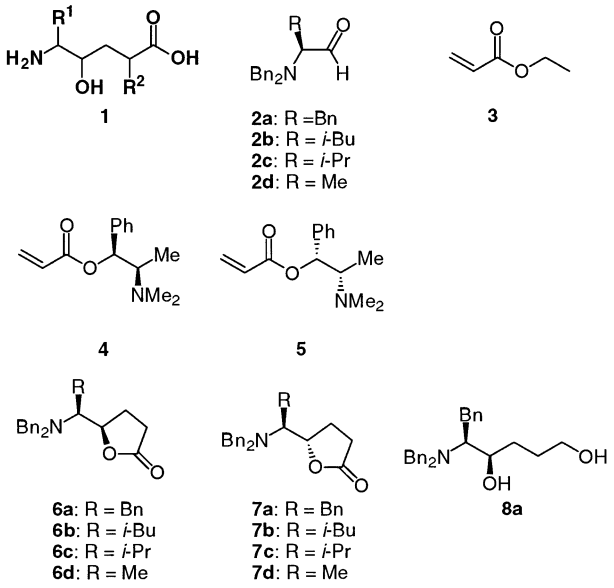

FIGURE 1.

Upon treatment of the mixture of the 2*S* dibenzylated amino aldehyde **2a** (R = Bn) and ethyl acrylate **3** with a THF solution of SmI_2 in the presence of *t*-BuOH at 0 °C for 2 h, the corresponding γ-aminoalkyl γ-butyrolactone was obtained as a mixture of diastereomers **6a** and **7a** in 50% yield. To determine the configuration of the ether carbon, the amino lactone was converted into the corresponding 1,4-diol (**8**) by reduction with $LiAlH_4$. The

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(4) Matsuda et al. reported the diastereoselective coupling reaction between the α-*Z*-protected amino ketones and crotonic esters: (a) Matsuda, F.; Kawatsura, M.; Dekura, F.; Shirahama, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2371. (b) Kawatsura, M.; Dekura, F.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 373.

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TABLE 1. SmI_2-Mediated Reaction of Amino Aldehyde with Acrylic Esters[a]

entry	ester	amino aldehyde	yield, %[b]	**6**:**7**[c]
1	**3**	**2a**	50	62:38
2	**3**	**2b**	27	53:47
3	**3**	**2c**	66	51:49
4	**3**	**2d**	36	52:48
5[d]	**3**	**2a**	22	60:40
6	**4**	**2a**	60	92:8
7	**4**	**2b**	40	84:16
8	**4**	**2c**	83	89:11
9	**4**	**2d**	32	90:10
10[d]	**4**	**2a**	30	68:32
11	**5**	**2a**	46	35:65
12	**5**	**2b**	22	42:58
13	**5**	**2c**	63	54:46
14	**5**	**2d**	22	65:35
15[d]	**5**	**2a**	13	64:36

[a] Conditions: SmI_2 (1.5 mmol), (*S*)-**2** (0.5 mmol), ester (0.6 mmol), *t*-BuOH (0.6 mmol), 0 °C, 2 h. [b] Isolated yield of a mixture of **6** and **7**. [c] Determined by ^{1}H NMR and/or HPLC. [d] HMPA (6 mmol) was added.

stereochemistry of **8a** was established by comparison of their ^{1}H NMR spectra with those separately prepared by the stereoselective allylation of **2a** with allyl organometallic compounds followed by hydroboration.[2c,5a] The chiral HPLC analysis (Chiralpack AD) of the amino lactone and **8** further demonstrated that the 4*R*,1′*S* isomer **6a** was preferably formed in the ratio **6a**:**7a** = 62:38. The reaction with other amino aldehydes **2b**−**d** (R = *i*-Bu, *i*-Pr, Me) gave the corresponding lactones as mixtures of almost 1:1 diastereomers in moderate yields. These results are summarized in Table 1 (entries 1−4). The chiral center of the amino aldehyde **2** poorly controlled the stereochemistry of the coupling reaction.

The use of the chiral acrylic ester derived from (1*S*,2*R*)-*N*-methylephedrine **4** instead of **3** produced a dramatic enhancement in the diastereoselectivity for the 4*R*,1′*S* amino lactones **6**. The reaction of each of the amino aldehydes **2a**−**d** with **4** afforded **6a**−**d** as the major products in high diastereomeric excess (up to 84% de) (Table 1, entries 6−9).[6] Compared to Nadin's 4*R*,1′*S* amino lactone synthesis, which involves a three-step transformation and separation of a diastereomeric mixture of the precursor, this samarium iodide method is much simpler and more efficient in accessing the 4*R*,1′*S* amino lactone with good yield and selectivity.[2a] As 4*R*,1′*S* isomers of amino lactones were obtained in one-step reactions in high diastereoselectivity, we next tried to prepare the 4*S*,1′*S* isomer by using (1*R*,2*S*)-*N*-methylephedrinyl acrylate **5**, which is an enantiomer of **4**. Although the reaction of **2a** with **5** afforded the 4*S*,1′*S* isomer **7a** as a major isomer, the diastereoselectivity was low (30% de) (Table 1, entry 11). The observed stereochemistry of the product seemed to be dependent on the alkyl substituent of the amino aldehydes **2a**−**d**; with the benzyl and isobutyl derivatives, the 4*S*,1′*S* isomer was preferably produced, while with the isopropyl and the methyl derivatives, the 4*R*,1′*S* isomer was preferably

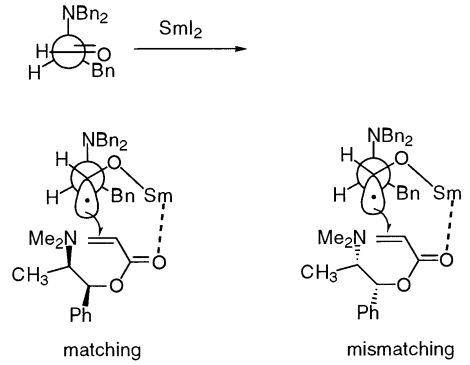

FIGURE 2. Transition state of the SmI_2-mediated coupling reaction of the α-amino aldehyde with the chiral acrylic ester.

TABLE 2. SmI_2-Mediated Reaction of (*R*)-2a with Acrylic Esters[a]

entry	ester	yield, %[b]	**9**:**10**[c]
1	**3**	56	58:42
2	**4**	45	38:62
3	**5**	59	92:8

[a] Conditions: SmI_2 (1.5 mmol), (*R*)-**2a** (0.5 mmol), ester (0.6 mmol), *t*-BuOH (0.6 mmol), 0 °C, 2 h. [b] Isolated yield of a mixture of **9** and **10**. [c] Determined by ^{1}H NMR and/or HPLC.

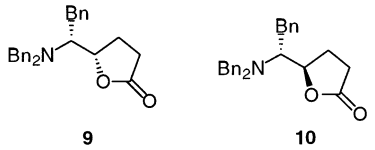

FIGURE 3.

obtained. In any event, the diastereoselectivities in the reaction with **5** were lower than those with **4**.

The stereochemistry of the amino lactone **6a** can be explained by the nonchelation control in the reaction with **3**; the amino nitrogen does not coordinate to the samarium atom.[5] This diastereoselection is similar to the samarium(II) iodide mediated iodomethylation of a chiral amino aldehyde; the stereocenter of (*S*)-**2** produces *R* stereochemistry to the ether carbon of the lactone ring.[7] The enhanced stereoselectivity in the reaction with the 1*S*,2*R* acrylate **4** may be explained by matching the stereoselection of the *S* chiral center of the amino carbon and the *S* chiral center of the ester carbon, as illustrated in Figure 2; chelation of the ester carbonyl oxygen to samarium should be involved in the high diastereoselection. This conformation should be the most preferable, thus leading to the *R* stereochemistry of the lactone ring. On the other hand, mismatching of the two chiral centers between the *S* amino carbon and the *R* ester carbon resulted in low diastereoselection. In the reaction of (*R*)-**2a**, the use of the 1*R*,2*S* acrylate **5** afforded enhanced diastereoselectivity leading to the *S* chiral center (**9**) to the lactone ring, while the 1*S*,2*R* ester **4** afforded low *R* selectivity due to the mismatched stereochemistry (Table 2, Figure 3).

The addition of HMPA to the reaction mixture of (*S*)-**2a** with acrylic esters **3**−**5** always gave the 4*R*,1′*S* isomer

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6a as a major isomer, independent of the stereochemistry of the acrylic ester with almost the same diastereoselectivity (**6a**:**7a** = (60:40)−(68:32)) (Table 1, entries, 5, 10, and 15). Since HMPA can strongly coordinate to the samarium atom and prevent organic molecules from chelating to the samarium atom,[8] the coupling reaction seemed to proceed without any chelation of samarium in the presence of HMPA; neither the amino nitrogen nor the carbonyl oxygen chelate to samarium.

Experimental Section

General Considerations. ^{1}H (400 MHz) and ^{13}C NMR spectra were recorded in $CDCl_3$, and the chemical shifts are reported in δ units downfield from tetramethylsilane, used as the internal standard. HPLC analyses were performed on Daicel Chiralcel OD and AD columns (0.46 mm, 25 cm), with with 2-propanol/*n*-hexane ((10:90)−(1:99)) as eluent, or on an ODS (Kanto Chemicals Ltd., Mightysil RP-18) column. Elemental analyses were carried out in the Microanalytical Laboratory at Chuo University. Column chromatography was performed using Merck silica gel 60.

Materials. Commercial dry THF was used without further purification. (1*S*,2*R*)- and (1*R*,2*S*)-*N*-methylephedrinyl acrylates **5** and **6** were prepared by the reaction of commercial acryloyl chloride with *N*-methylephedrine.[6a] Enantiomerically pure (2*S*)-*N*,*N*-dibenzylamino aldehydes are prepared by the reported method.[9]

Reaction of (1*S*,2*R*)-*N*-Methylephedrinyl Acrylate 4 with (2*S*)-*N*,*N*-Dibenzyl-3-phenylpropanal (2a). Under a nitrogen atmosphere, samarium powder (99.9%; 225 mg, 1.5 mmol) was placed in a 50 mL Schlenk tube equipped with a magnetic stirring bar. A dry THF (10 mL) solution of diiodomethane (400 mg, 1.5 mmol) was added using a syringe through a septum. The mixture was then stirred for 2 h at room temperature, and the samarium(II) iodide solution was obtained as a deep green solution. The Schlenk tube was cooled in a ice bath, and a mixture of **4** (140 mg, 0.6 mmol), **2a** (165 mg, 0.5 mmol), and *t*-BuOH (42 mg, 0.6 mmol) in THF (1 mL) was slowly injected over a period of 5 min. The resulting solution is stirred at 0 °C for 2 h, during which time the deep green color of the solution faded. The solution was hydrolyzed with 20 mL of saturated ammonium chloride. Passing it through Celite filtered off the insoluble part, and the aqueous phase was extracted with three 20 mL portions of ethyl acetate. The organic phase was washed with brine and then dried over magnesium sulfate. The solvent was removed under reduced pressure to give the crude product as a pale yellow oil. ^{1}H NMR measurement of the crude product revealed that the product was obtained as a mixture of diastereomers in the ratio **6a**:**7a** = 92:8. The product was isolated by preparative TLC on silica gel (2:1 hexane/ethyl acetate as eluent) to afford the pure (5*R*,1′*S*)-5-(1′-(dibenzylamino)-2′-phenylethyl)dihydrofuran-2(3*H*)-one (**6a**) as a pale yellow liquid (108 mg, 0.28 mmol, 56% yield based on **2a**). The 82% diastereomeric excess of the product was further confirmed by conversion to the corresponding diol **8a** by HPLC using a chiral column (Chiralpack AD).

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(5*R*,1′*S*)-5-(1′-(Dibenzylamino)-2′-phenylethyl)dihydrofuran-2(3*H*)-one (6a). $[\alpha]^{25}_D = -6.5°$ (c = 0.46, $CHCl_3$) (lit.[2c] +0.2°). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.8−1.9 (m, 1H), 2.2−2.5 (m, 3H), 2.9−3.1 (m, 3H, including CHN and CH_2Ph), 3.70 (s, 4H), 4.65−4.75 (m, 1H), 7.1−7.4 (m, 15 H), ^{13}C NMR: δ_C 26.4, 28.1, 32.4, 54.3, 62.3, 80.8, 126.1, 126.9, 128.1, 128.2, 128.6, 128.7, 129.1, 129.5, 139.1, 139.9, 177.1. Anal. Calcd for $C_{26}H_{27}NO_2$: C, 81.01; H, 7.06; N, 3.63. Found: C, 80.98; H, 7.36; N, 3.57. Data for the minor isomer (5*S*,1′*S*)-5-(1′-(dibenzylamino)-2′-phenylethyl)dihydrofuran-2(3*H*)-one (**7a**) are as follows. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.3−2.6 (m, 4H), 2.8−3.2 (m, 3H, including CHN and CH_2Ph), 3.64 (d, 2H, J = 13.5 Hz), 4.05 (d, 2H, J = 13.5 Hz), 4.4−4.5 (m, 1H), 7.1−7.3 (m, 15H).

(5*R*,1′*S*)-5-(1′-(Dibenzylamino)-3′-methylbutyl)dihydrofuran-2(3*H*)-one (6b). $[\alpha]^{25}_D = -42.2°$ (c = 0.38, $CHCl_3$) (lit.[2c] −43.9°). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.61 (d, 3H, J = 6.4 Hz), 0.83 (d, 3H, J = 6.4 Hz), 1.1−1,3 (m, 1H), 1.5−2.0 (m, 4H), 2.2−2.55 (m, 2H), 2.6−2.7 (m, 1H), 3.55 (d, 2H, J = 13.8 Hz), 3.75 (d, 2H, J = 13.8 Hz), 4.6−4.7 (m, 1H), 7.1−7.3 (m, 10H). ^{13}C NMR: δ_C 22.2, 23.4, 24.7, 26.5, 28.2, 35.4, 54.4, 58.1, 80.4, 127.0, 128.2, 128.9, 139.6, 177.4. HRMS: m/z calcd for $C_{23}H_{29}NO_2$ 352.2277 [M + H], found 352.2185. Data for the minor isomer (5*S*,1′*S*)-5-(1′-(dibenzylamino)-3′-methylbutyl)dihydrofuran-2(3*H*)-one (**7b**) are as follows. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (distinguished signals) 0.47 (d, 3H, J = 6.45 Hz), 0.80 (d, 3H, J = 6.45 Hz), 3.64 (d, 2H, J = 13.18 Hz), 3.69 (d, 2H, J = 13.18 Hz), 4.55 (dt, 1H, J = 7.32, 7.92 Hz).

(5*R*,1′*S*)-5-(1′-(Dibenzylamino)-2′-methylpropyl)-dihydrofuran-2(3*H*)-one (6c). $[\alpha]^{25}_D = -12.8°$ (c = 0.46, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.06 (d, 3H, J = 7.03 Hz), 1.10 (d, 3H, J = 7.0 Hz), 1.95−2.05 (m, 1H), 2.2−2.3 (m, 4H), 2.4−2.5 (m, 1H), 3.59 (d, 2H, J = 13.4 Hz), 3.71 (d, 2H, J = 13.4 Hz), 4,76 (dt, 1H, J = 7.6, 6.8 Hz). ^{13}C NMR: δ_C 19.2, 23.1, 25.1, 27.1, 27.8, 54.5, 64.2, 79.2, 127.0, 128.2, 129.2, 139.2, 177.3. Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.52; H, 8.36; N, 4.27. Data for the minor isomer (5*S*,1′*S*)-5-(1′-(dibenzylamino)-2′-methylpropyl)dihydrofuran-2(3*H*)-one (**7c**) are as follows. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.87 (d, 3H, J = 6.81 Hz), 1.03 (d, 3H, 7.03 Hz), 1.5−1.6 (m, 1H), 1.9−2.1 (m, 3H), 2.5−2.6 (m, 3H, including CHN), 3.82 (d, 2H, J = 13.18 Hz), 3.89 (d, 2H, J = 13.4 Hz), 4.81 (dt, 1H, J = 8.4, 6.8 Hz).

(5*R*,1′*S*)-5-(1′-(Dibenzylamino)ethyl)dihydrofuran-2(3*H*)-one (6d). $[\alpha]^{25}_D = +20.7°$ (c = 0.34, $CHCl_3$) (lit.[2c] +24.0°). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.20 (d, 3H, J = 6.8 Hz), 1.9−2.1 (m, 1H), 2.2−2.4 (m, 3H), 2.69 (quint, 1H, J = 7.0 Hz), 3.44 (d, 2H, J = 13.8 Hz), 3.72, (d, 2H, J = 13.8 Hz), 4.42 (dt, 1H, J = 7.0, 7.3 Hz), 7.2−7.4 (m, 10H). ^{13}C NMR: δ_C 8.8, 26.1, 28.1, 54.2, 56.3, 82.6, 127.0, 128.3, 128.8, 139.4, 177.3. HRMS: m/z calcd for $C_{20}H_{23}NO_2$ 310.1807 [M + H], found 310.1580. Data for the minor isomer (5*S*,1′*S*)-5-(1′-(dibenzylamino)ethyl)-dihydrofuran-2(3*H*)-one (**7d**) are as follows. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (distinguished signals) 4.1−4.2 (m, 1H).

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Supporting Information Available: Figures giving ^{1}H and ^{13}C NMR spectra of the major products **6a**−**d.** This material is available free of charge via the Internet at http/pubs.acs.org.

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