Urethane group directed reductive couplings mediated by SmI_2

Fuyuhiko Matsuda,* † Motoi Kawatsura, Fumiko Dekura and Haruhisa Shirahama

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan. E-mail: fmatsuda@ees.hokudai.ac.jp

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The SmI_2-induced ketone–olefin coupling reactions of α-(alkoxycarbonyl)amino ketones **1** and **3** with methyl, ethyl, isopropyl, and *tert*-butyl crotonate took place with high stereocontrol about the new chiral centers providing the *syn*-1,2-amino alcohol products, *syn-trans*-γ-lactones **2** and **4**, in excellent yields. Apparently, the stereochemical course of these reductive couplings is stereocontrolled by chelation of the Sm(III) cations attached to the resulting ketyl radicals with the urethane groups. Stereoselectivity increased as the size of the alkyl group of the esters of crotonic acid increased. In particular, **2** and **4** were almost exclusively obtained when the SmI_2-induced couplings of **1** and **3** were carried out with *tert*-butyl crotonate. Interestingly, the hydroxy group-directed couplings induced by SmI_2 of the α-hydroxy ketone **11** with methyl, ethyl, and isopropyl crotonate proceeded with a complete reversal of diastereoselectivity, almost exclusively providing the *syn*-1,2-diol product, *syn-cis*-γ-lactone **12**.

Introduction

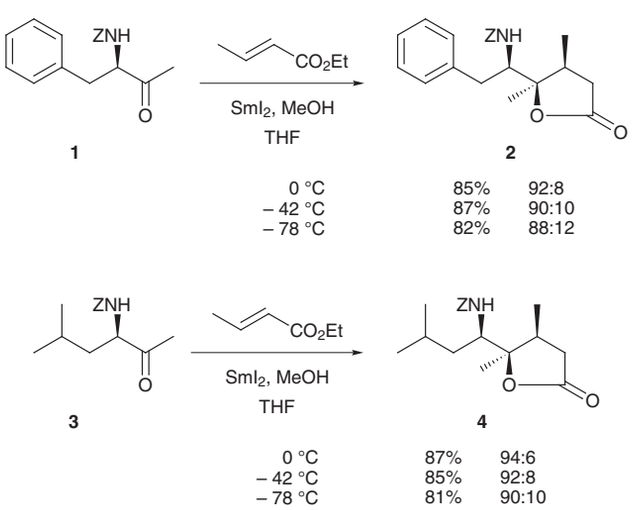
Samarium(II) iodide (SmI_2) has become an exceedingly reliable reagent for promoting reductive coupling reactions difficult to accomplish by any other existing methodologies.[1] For example, Barbier reactions, Reformatsky reactions, ketone–olefin reductive couplings, and pinacol couplings have been reported using SmI_2 as a reagent substitute. Previous research from this laboratory demonstrated the powerful influence of appropriately positioned hydroxy groups in facilitating the SmI_2-promoted reductive couplings and controlling the stereochemical outcome.[2–4] During these hydroxy-directed transformations, excellent diastereoselectivity was achieved in all cases, and the sense of the stereoselectivity was in full accord with a chelation-control model. In the proposed model, the observed stereochemistry of the reaction product can be explained by assuming that a cyclic ketyl radical is generated during initial single-electron transfer from SmI_2 to the carbonyl group of the starting material. This radical species arises from chelation of the Sm(III) cation attached to the ketyl with the hydroxy group. It is particularly noteworthy that the intermolecular version of the hydroxy group-directed SmI_2-mediated ketone–olefin coupling takes place with nearly complete diastereoselectivity.[3] Although many SmI_2-mediated annulation reactions provided an efficient route to polyoxygenated carbocycles and heterocycles with high stereochemical control, few stereocontrolled SmI_2-induced intermolecular couplings have been reported.[5]

In connection with our interest in the development of stereoselective intermolecular carbon–carbon bond formation reactions induced by SmI_2, we have evaluated the reductive couplings of several (alkoxycarbonyl)amino ketones. Eventually, it has been found that the intermolecular ketone–olefin couplings induced by SmI_2 of α-(alkoxycarbonyl)amino ketones with α,β-unsaturated esters are also enhanced and chelation-controlled by the urethane groups.[6,7] We describe here a new type of stereoselective intermolecular coupling reaction promoted by SmI_2. The complementary diastereoselectivity observed in the ketyl–olefin coupling reactions of the α-(alkoxycarbonyl)amino and α-hydroxy ketones is also reported.

† *Present address*: Division of Material Science, Graduate School of Environmental Earth Science, Hokkaido University, Sapporo 060-0810, Japan.

Results and discussion

First, the ketone–olefin coupling reactions of the (±)-α-(benzyloxycarbonyl)amino ketones **1** and **3** were performed utilizing ethyl crotonate as the ketyl radical acceptor (Scheme 1). The ketones **1** and **3** were prepared from (±)-*N*-(benzyloxycarbonyl)phenylalaninol and (±)-*N*-(benzyloxycarbonyl)-leucinol in 55% and 69% overall yields, respectively, by the sequence of (1) Swern oxidation, (2) an addition with MeLi, and (3) oxidation with PDC.



Scheme 1

As revealed in Scheme 1, the SmI_2-promoted coupling reactions of **1** and **3** very cleanly took place in the presence of *an almost equimolar amount* (1.5 equiv.) of ethyl crotonate to afford the *syn*-1,2-amino alcohol products, γ-lactones **2** and **4**, respectively, in excellent yields with good diastereoselectivity at three contiguous stereocenters. In each case of the reductive coupling of **1** and **3**, a small amount of another diastereoisomeric γ-lactone was obtained. No other stereoisomers could be detected from 400 MHz ^{1}H-NMR spectra or chromatographic analysis. While these minor diastereoisomers had the *syn*-1,2-amino alcohol stereochemistry, the relative configuration (*cis*) between the vicinal methyl groups of the minor

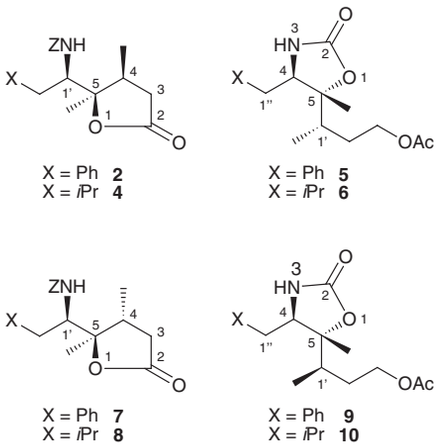


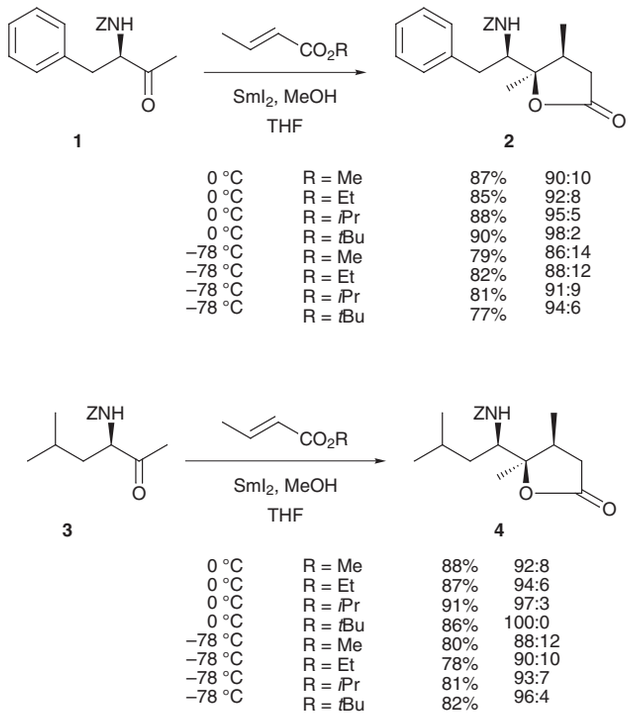
Fig. 1

isomers is opposite to that (*trans*) of the major diastereoisomers, *syn-trans*-γ-lactones **2** and **4**. Interestingly, an increase in reaction temperature resulted in increased stereoselectivity of these coupling reactions. Thus, the diastereoisomeric ratios of the *syn-trans*-γ-lactones **2** and **4** to their minor diastereoisomers (*syn-cis*-γ-lactones) increased to 92:8 and 94:6 when the coupling reactions were carried out at 0 °C, and ratios of 88:12 and 90:10 were obtained at a reaction temperature of −78 °C. As previously described, the SmI_2-induced, intermolecular ketone–olefin couplings chelation-controlled by α-hydroxy and β-hydroxy groups were more stereoselective at higher temperatures in many cases.[3,8]

The relative stereochemistry of the major *syn-trans*-γ-lactones **2**, **4** and the minor *syn-cis*-γ-lactones **7**, **8** was assigned by the 2D-NOESY experiments on the tetrahydrofuran-2-ones **2**, **4**, **7**, **8**, and the 1,3-oxazolidin-2-ones **5**, **6**, **9**, **10** derived from **2**, **4**, **7**, **8** (Fig. 1). In each case of the 2D-NOESY experiments on **2** and **4**, 4-H gave an NOE correlation peak with 5-Me, while 4-Me also gave an NOE with 1′-H (furanone numbering), arguing that the two vicinal methyl groups of **2** and **4** were situated *trans* on the γ-lactone rings. On the other hand, the *cis* relative configuration between the vicinal methyl groups of **7** and **8** was determined from NOE correlations from 4-H to 1′-H and from 4-Me to 5-Me in the 2D-NOESY spectra of **7** and **8**. The 2D-NOESY analyses of **5**, **6**, **9**, and **10** revealed that NOE correlations were observed between 4-H and 1′-H and between 4-CH_2 (1″-H_2) and 5-Me (oxazolidinone numbering) in all cases. These NMR data confirmed that all of the coupling products **2**, **4**, **7**, and **8** possessed the *syn*-1,2-amino alcohol stereochemistry.

In addition to ethyl crotonate, the use of methyl, isopropyl, and *tert*-butyl crotonate was also examined as the ketyl radical acceptor in the SmI_2-mediated coupling reactions of the α-(benzyloxycarbonyl)amino ketones **1** and **3**. The results obtained from these ketone–olefin couplings are summarized in Scheme 2. All of these reactions occurred in excellent yields comparable to those recorded for ethyl crotonate. Diastereoselectivity increased as the size of the alkyl group of the esters of crotonic acid increased. In particular, the *syn-trans*-γ-lactones **2** and **4** were obtained in product ratios (*trans*:*cis*) of 98:2 and 100:0,[9] respectively, upon performing the SmI_2-induced couplings of **1** and **3** with *tert*-butyl crotonate at 0 °C. Remarkably, a single stereochemical result was obtained from four possible products. Again, lowering the reaction temperature from 0 to −78 °C led to a drop in diastereoselectivity in all cases.

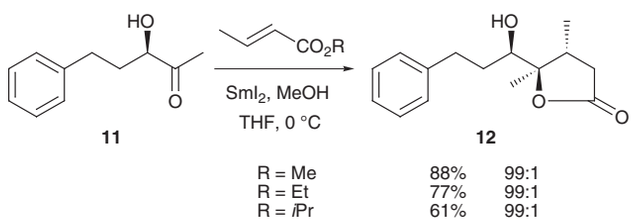
The optimized reaction conditions for the ketone–olefin couplings of **1** and **3** involved the addition of a 0.1 M solution of SmI_2 in THF (2.5 equiv.) to a solution of **1** or **3** and methyl, ethyl, isopropyl, or *tert*-butyl crotonate (1.5 equiv.) in a 2:1 mixture of THF and MeOH at 0 °C.[10] The coupling reactions were completed within 5 min utilizing the optimized reaction



Scheme 2

conditions. The reaction mixtures were subsequently quenched with saturated aqueous $NaHCO_3$. A simple extractive workup, followed by chromatographic purification, provided the desired 1,2-amino alcohol products. Even at −78 °C, the reactions readily occurred without the need for HMPA as an additive, although a promoter such as HMPA was usually required to promote efficient intermolecular ketyl–olefin couplings at low temperature.[11] Therefore, not only do the urethane groups control the stereochemistry of the reductive coupling reactions, but they have the added function of accelerating the reaction as well.

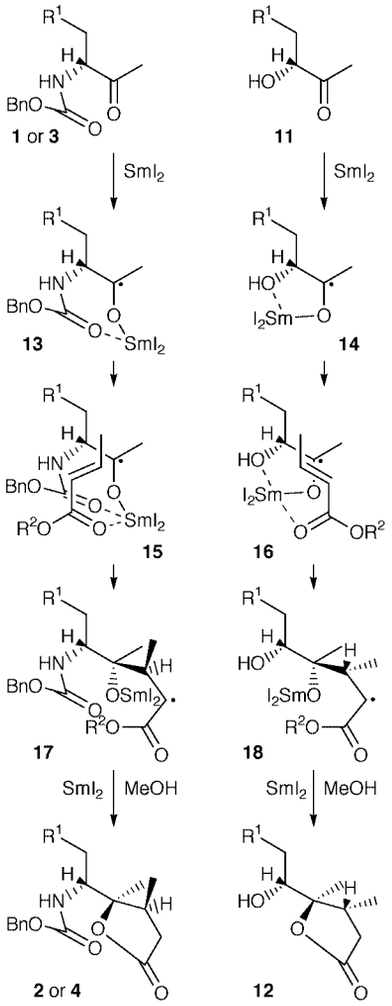
Curiously, the hydroxy-directed intermolecular couplings induced by SmI_2 of the α-hydroxy ketone **11** with methyl, ethyl, and isopropyl crotonate proceeded with a complete reversal of diastereoselectivity to almost exclusively provide the *syn*-1,2-diol product, *syn-cis*-γ-lactone **12** as illustrated in Scheme 3.[3a,12,13] Although the diastereofacial preference of the



Scheme 3

α-(benzyloxycarbonyl)amino ketones **1** and **3** in the ketone–olefin couplings is the same as that seen in the reactions of the α-hydroxy ketone **11**, the relative stereochemistry about the two new stereogenic centers of the *syn-trans*-γ-lactones **2** and **4** was opposite to that of the *syn-cis*-γ-lactone **12**. From a synthetic point of view, this is highly advantageous because it provides entry into manifold diastereoisomeric products. The results also have mechanistic implications.

The sense of the complementary diastereoselectivities may be explained by assuming a chelation-control model as depicted in Scheme 4. Thus, after single-electron transfer from SmI_2 to the ketone group of the starting α-(alkoxycarbonyl)amino ketones **1**, **3** and α-hydroxy ketone **11**, chelation of the Sm(III) cations generated during the initial reduction process with



Scheme 4

the α-(alkoxycarbonyl)amino and α-hydroxy groups gives the requisite species for construction of the 7-membered ring ketyl **13** and 5-membered ring ketyl **14**, respectively. The esters of crotonic acid approach from the sterically less hindered direction (β-face) of the cyclic ketyl radicals, and the carbon–carbon bond formation reactions proceed with excellent diastereoselectivity. Subsequent reduction of the resulting radicals **17** and **18** by the second equiv. of SmI_2, protonation of the Sm(III) enolate with MeOH, and simultaneous γ-lactonization would produce the observed *syn*-1,2-amino alcohol products **2**, **4** and the *syn*-1,2-diol product **12**. The principal difference between the cyclic ketyls **13** and **14** is the positioning of the Sm(III) cation attached to the ketyl radical. Thus, given the hypothesis that the carbon–carbon bond formation reactions proceed involving the coordination of the ester carbonyl groups to the Sm(III) cations of the cyclic ketyl radicals **13** and **14** as shown in **15** and **16**, the observed dramatic reversal of facial preference of the esters of the crotonic acid may be accounted for. Inanaga *et al.* also reasonably postulated that a contributing factor governing the high diastereoselectivity of the SmI_2-induced coupling reactions of cyclohexanecarbaldehyde and octanal with methyl crotonate is the cooperative Sm(III) cation ligation of both the ketyl and ester.[5a,b]

Conclusion

In summary, it has been established that the SmI_2-promoted ketyl–olefin couplings are accelerated and stereocontrolled by the urethane groups incorporated within the starting α-(alkoxycarbonyl)amino ketones. The reactions proceed in good yields with high stereochemical control at three contiguous asymmetric centers. The sense of the stereoselectivity was in full accord with a chelation-control model, similar to that proposed during the hydroxy group-directed couplings induced by SmI_2.[2–4] This result implies that urethane groups effectively direct the SmI_2-mediated ketyl radical couplings as well as the hydroxy groups.[7]

Interestingly, the hydroxy group-directed couplings induced by SmI_2 of the α-hydroxy ketone proceeded with a complete reversal of the relative stereochemistry about the two new stereogenic centers. The chelation-control model may also explain the complementary diastereoselectivity. From a synthetic point of view, the observed stereocomplementarity is highly advantageous because it provides entry into the divergent syntheses of diastereoisomeric products.

Experimental

Melting points were determined in an open capillary tube and are uncorrected. IR spectra were recorded on a JASCO IR-S spectrometer in an NaCl cell. ^{1}H- and ^{13}C-NMR Spectra were recorded on a JNM-FX-400 (400 and 100 MHz) spectrometer. Chemical shifts are reported in ppm downfield from the peak of Me_4Si as an internal standard. Splitting patterns are designated as s, d, t, q, and br; these symbols indicate singlet, doublet, triplet, quartet, and broad, respectively. Mass spectra were obtained on a JEOL Model JMS-DX 300, a JMS-DX 303, and a 01SG-2 spectrometer.

Unless otherwise noted, non-aqueous reactions were carried out under an Ar atmosphere. Dichloromethane (CH_2Cl_2) was distilled from CaH_2. Methanol (MeOH) was distilled from $Mg(OMe)_2$. Tetrahydrofuran (THF) was distilled immediately prior to use from Na metal–benzophenone ketyl under Ar atmosphere. (±)-2-[(Benzyloxycarbonyl)amino]-3-phenylpropan-1-ol (*N*-Z-phenylalaninol) and (±)-2-[(benzyloxycarbonyl)amino]-4-methylpentan-1-ol (*N*-Z-leucinol) were prepared in three steps according to known procedures[14] starting from (±)-phenylalanine and (±)-leucine, respectively. All other commercially obtained reagents were used as received. Analytical and preparative thin layer chromatographies were carried out using pre-coated silica gel plates (Macherey-Nagel DC-Fertigplatten SIL G-25 UV_{254}). The silica gel used for column chromatographies was Merck Kieselgel 60 Art 7734.

(±)-3-[(Benzyloxycarbonyl)amino]-4-phenylbutan-2-one 1

To a solution of $(COCl)_2$ (0.430 mL, 4.93 mmol) in CH_2Cl_2 (8.0 mL) cooled at −50 °C was added a solution of DMSO (0.770 mL, 10.9 mmol) in CH_2Cl_2 (2.0 mL) and a solution of (±)-*N*-Z-phenylalaninol (1.13 g, 3.96 mmol) in CH_2Cl_2 (2.0 mL). Stirring was continued at −50 °C for 15 min and Et_3N (3.00 mL, 21.5 mmol) was added. The reaction mixture was warmed to room temperature over 1 h and diluted with ether. The ethereal solution was washed with H_2O and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was dissolved in THF (10 mL) and cooled to 0 °C. To this solution was added a 1.00 M THF solution of MeMgBr (6.00 mL, 6.00 mmol). The mixture was stirred at 0 °C for 3 h, quenched with saturated aqueous NH_4Cl, and extracted with AcOEt. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt–hexane, 20 : 80) to give (±)-3-[(benzyloxycarbonyl)amino]-4-phenylbutan-2-ol (0.925 g, 78%) as a 1 : 1 diastereomeric mixture.

To a suspension of PDC (2.48 g, 6.59 mmol) and 4 Å molecular sieves (2.48 g) in CH_2Cl_2 (6.0 mL) at room temperature was added a solution of the amino alcohol (0.925 g, 3.09 mmol) in CH_2Cl_2 (2.0 mL). After stirring at room temperature for 30 min, ether was added and the mixture was filtered through a plug of Celite. The filtrate was concentrated *in vacuo*, and purification

by silica gel column chromatography (AcOEt–hexane, 10:90) afforded **1** (0.643 g, 70%) as white crystals, mp 63–64 °C (Found: C, 72.67; H, 6.48; N, 4.73. $C_{18}H_{19}NO_3$ requires C, 72.70; H, 6.44; N, 4.71%); ν_{max} (Nujol)/cm^{-1} 3320, 1725, 1690, 1540, 1310, 1260, 1205, 1150, 1065, 1005; δ_H ($CDCl_3$) 2.15 (3H, s), 3.03, 3.07 (each 1H, dd, *J* 6.5 and 12.3 Hz), 4.63 (1H, q, *J* 6.5 Hz), 5.08, 5.09 (each 1H, d, *J* 12.1 Hz), 5.38 (1H, d, *J* 6.5 Hz), 7.09–7.39 (10H, m); δ_C ($CDCl_3$) 27.9, 37.5, 61.1, 66.9, 127.1, 128.0, 128.2, 128.5, 128.7, 129.2, 135.7, 136.3, 155.7, 206.2; *m*/*z* (EI) 297 (M^+), 254 (M^+ − Ac).

(±)-3-[(Benzyloxycarbonyl)amino]-5-methylhexan-2-one 3

Swern oxidation of (±)-*N*-Z-leucinol, addition of MeMgBr, and PDC oxidation in accord with the procedure previously described furnished **3** in 69% yield as white crystals, mp 107–108 °C (Found: C, 68.31; H, 8.10; N, 5.37. $C_{15}H_{21}NO_3$ requires C, 68.41; H, 8.04; N, 5.32%); ν_{max} (Nujol)/cm^{-1} 3310, 1725, 1680, 1545, 1350, 1315, 1270, 1225, 1190, 1120, 980; δ_H ($CDCl_3$) 0.93, 0.98 (each 3H, d, *J* 6.7 Hz), 1.38 (1H, ddd, *J* 4.8, 9.9, and 13.5 Hz), 1.59 (1H, ddd, *J* 3.8, 8.6, and 13.5 Hz), 1.72 (1H, m), 2.21 (3H, s), 4.41 (1H, dt, *J* 4.8 and 8.6 Hz), 5.10 (2H, s), 5.26 (1H, d, *J* 8.6 Hz), 7.29–7.39 (5H, m); δ_C ($CDCl_3$) 21.7, 23.3, 24.9, 27.0, 40.6, 58.9, 67.0, 128.0, 128.2, 128.5, 136.3, 156.1, 207.4; *m*/*z* (EI) 263 (M^+), 220 (M^+ − Ac).

Preparation of THF solution of SmI_2

To a slurry of Sm metal powder (2.00 g, 13.3 mmol) in THF (100 mL) was added CH_2I_2 (0.900 mL, 11.2 mmol). The mixture was stirred at room temperature for 3 h. The resulting blue solution was used directly to effect the following reductive couplings.

General procedure for reductive coupling of α-(benzyloxycarbonyl)amino ketone with crotonic acid ester

To a solution of **1** or **3** (0.067 mmol) and methyl, ethyl, isopropyl, or *tert*-butyl crotonate (0.101 mmol) in a mixture of THF (0.70 mL) and MeOH (0.35 mL) was added 0.10 M THF solution of SmI_2 (1.68 mL, 0.168 mmol). After stirring for 5 min, TLC analysis of the reaction mixture showed complete consumption of the starting ketone. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ether. The combined ethereal extracts were washed with H_2O and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (1.0 mL), and CSA (5.00 mg, 0.022 mmol) was added. The mixture was stirred at room temperature for 12 h and diluted with ether. The ethereal solution was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The diastereoisomeric ratios (*trans*:*cis*) were determined from the 400 MHz ^{1}H-NMR spectra of the crude product. Purification by preparative silica gel TLC (AcOEt–PhMe, 30:70) gave the *syn-cis*- and *syn-trans*-lactones.

(4*S,5*R**,1′*R**)-5-[1-(Benzyloxycarbonyl)amino-2-phenylethyl]tetrahydro-4,5-dimethylfuran-2-one (*syn-trans*-γ-lactone) 2.** Colorless oil (Found: C, 71.96; H, 6.89; N, 3.68. $C_{22}H_{25}NO_4$ requires C, 71.91; H, 6.86; N, 3.81%); ν_{max} (neat)/cm^{-1} 3290, 1775, 1705, 1530, 1255, 1135, 1080, 1030, 975; δ_H ($CDCl_3$) 1.21 (3H, d, *J* 7.0 Hz), 1.51 (3H, s), 2.39 (1H, dd, *J* 10.4 and 16.5 Hz), 2.49 (1H, m), 2.63 (2H, m), 3.11 (1H, dd, *J* 3.5 and 13.6 Hz), 4.22 (1H, dt, *J* 3.5 and 10.9 Hz), 4.57 (1H, d, *J* 10.9 Hz), 4.77, 4.81 (each 1H, d, *J* 12.3 Hz), 7.07–7.32 (10H, m); δ_C ($CDCl_3$) 13.0, 23.8, 24.8, 37.0, 37.7, 40.3, 60.5, 88.3, 127.1, 128.0, 128.2, 128.5, 128.7, 129.1, 135.7, 136.3, 155.8, 175.9; *m*/*z* (EI) 367 (M^+), 276 (M^+ − CH_2Ph).

(4*R,5*R**,1′*R**)-5-[1-(Benzyloxycarbonyl)amino-2-phenylethyl]tetrahydro-4,5-dimethylfuran-2-one (*syn-cis*-γ-lactone) 7.** Colorless oil (Found: C, 72.01; H, 6.77; N, 3.72. $C_{22}H_{25}NO_4$ requires C, 71.91; H, 6.86; N, 3.81%); ν_{max} (neat)/cm^{-1} 3290, 1775, 1705, 1530, 1255, 1135, 1080, 1030, 975; δ_H ($CDCl_3$) 1.10 (3H, d, *J* 7.0 Hz), 1.36 (3H, s), 2.31 (1H, dd, *J* 11.9 and 17.1 Hz), 2.58 (1H, dd, *J* 7.2 and 17.1 Hz), 2.67 (2H, m), 3.21 (1H, dd, *J* 4.1 and 14.0 Hz), 4.08 (1H, dt, *J* 4.1 and 9.9 Hz), 4.68 (1H, d, *J* 9.9 Hz), 4.70, 4.82 (each 1H, d, *J* 12.2 Hz), 7.06–7.32 (10H, m); *m*/*z* (EI) 367 (M^+), 276 (M^+ − CH_2Ph).

(4*S,5*R**,1′*R**)-5-[1-(Benzyloxycarbonyl)amino-3-methylbutyl]tetrahydro-4,5-dimethylfuran-2-one (*syn-trans*-γ-lactone) 4.** White solid, mp 104–105 °C (Found: C, 68.46; H, 8.12; N, 4.11. $C_{19}H_{27}NO_4$ requires C, 68.44; H, 8.16; N, 4.20%); ν_{max} (Nujol)/cm^{-1} 3290, 1780, 1695, 1545, 1270, 1140, 1080, 1040, 950; δ_H ($CDCl_3$) 0.91, 0.93 (each 3H, d, *J* 6.8 Hz), 1.17 (3H, d, *J* 7.0 Hz), 1.29 (1H, ddd, *J* 3.2, 10.4, and 14.1 Hz), 1.36 (3H, s), 1.39 (1H, ddd, *J* 2.7, 11.2, and 14.1 Hz), 1.58 (1H, m), 2.32 (1H, dd, *J* 7.0 and 17.1 Hz), 2.41 (1H, dquintet, *J* 8.2 and 7.0 Hz), 2.65 (1H, dd, *J* 8.2 and 17.1 Hz), 4.02 (1H, dt, *J* 2.7 and 10.4 Hz), 4.54 (1H, d, *J* 10.4 Hz), 5.09, 5.11 (each 1H, d, *J* 12.0 Hz), 7.28–7.38 (5H, m); δ_C ($CDCl_3$) 13.0, 21.4, 23.4, 23.9, 24.4, 37.7, 40.3, 40.8, 52.4, 67.0, 89.5, 128.1, 128.2, 128.5, 136.4, 156.0, 176.0; *m*/*z* (EI) 333 (M^+).

(4*R,5*R**,1′*R**)-5-[1-(Benzyloxycarbonyl)amino-3-methylbutyl]tetrahydro-4,5-dimethylfuran-2-one (*syn-cis*-γ-lactone) 8.** Colorless oil (Found: C, 68.55; H, 8.09; N, 4.25. $C_{19}H_{27}NO_4$ requires C, 68.44; H, 8.16; N, 4.20%); ν_{max} (neat)/cm^{-1} 3290, 1780, 1695, 1545, 1270, 1140, 1080, 1040, 950; δ_H ($CDCl_3$) 0.90, 0.92 (each 3H, d, *J* 6.8 Hz), 1.06 (3H, d, *J* 7.0 Hz), 1.22 (3H, s), 1.45 (2H, m), 1.63 (1H, m), 2.26 (1H, m), 2.55 (2H, m), 3.81 (1H, dt, *J* 3.6 and 10.3 Hz), 4.65 (1H, d, *J* 10.3 Hz), 5.09, 5.13 (each 1H, d, *J* 12.5 Hz), 7.29–7.39 (5H, m); *m*/*z* (EI) 333 (M^+).

(4*R**,5*R**,1′*S**)-4-Benzyl-5-(3-acetoxy-1-methylpropyl)-5-methyl-1,3-oxazolidin-2-one 5

The following describes the general procedure for the synthesis of the 1,3-oxazolidin-2-ones from the *syn*-γ-lactones (tetrahydrofuran-2-ones). To a solution of the *syn-trans*-γ-lactone **2** (35.0 mg, 0.095 mmol) in THF (1.0 mL) cooled at 0 °C was added $LiAlH_4$ (20.0 mg, 0.527 mmol). The reaction was stirred at 0 °C for 5 min and quenched with AcOEt. The mixture was treated with successive additions of H_2O (0.02 mL), 15% aqueous NaOH (0.02 mL), and H_2O (0.06 mL). The resultant white precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was diluted with a 1.0 M MeOH solution of NaOH (0.30 mL). Stirring was continued at ambient temperature for 5 h and AcOEt was added. The resulting solution was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford a crude product containing 4-benzyl-5-(3-hydroxy-1-methylpropyl)-5-methyl-1,3-oxazolidin-2-one. The crude product was dissolved in pyridine (0.50 mL) and treated with DMAP (1.00 mg, 8.19 μmol) and Ac_2O (90.0 μL, 0.954 mmol). After stirring at room temperature for 30 min, the mixture was diluted with ether. The ethereal solution was washed with saturated aqueous $CuSO_4$, H_2O, saturated aqueous $NaHCO_3$, and brine, and dried over Na_2SO_4. Concentration *in vacuo* and purification by silica gel column chromatography (AcOEt–PhMe, 20:80) furnished **7** (20.5 mg, 70%) as a colorless oil (Found: C, 66.56; H, 7.52; N, 4.61. $C_{17}H_{23}NO_4$ requires C, 66.86; H, 7.59; N, 4.59%); ν_{max} (neat)/cm^{-1} 3280, 2950, 1755, 1495, 1455, 1390, 1370, 1245, 1090, 1035, 990; δ_H ($CDCl_3$) 1.09 (3H, d, *J* 7.0 Hz), 1.41 (3H, s), 1.42 (1H, m), 1.93 (2H, m), 2.06 (3H, s), 2.70 (1H, dd, *J* 11.0 and 13.5 Hz), 2.85 (1H, dd, *J* 3.1 and 13.5 Hz), 3.77 (1H, dd, *J* 3.1 and 11.0 Hz), 4.09 (1H, ddd, *J* 6.4, 8.3, and 10.9 Hz), 4.22 (1H, ddd, *J* 4.5, 7.4, and 10.9 Hz), 4.79 (1H, br s), 7.18 (2H, d, *J* 8.1 Hz), 7.28 (1H, t, *J* 8.1 Hz), 7.35 (2H, t, *J* 8.1 Hz); *m*/*z* (EI) 246 (M^+ − OAc), 214 (M^+ − CH_2Ph).

(4*R,5*R**,1′*R**)-4-Benzyl-5-(3-acetoxy-1-methylpropyl)-5-methyl-1,3-oxazolidin-2-one 9**

Following the procedure previously described, the title compound was prepared from the *syn-cis*-γ-lactone **7** in 68% yield as a colorless oil (Found: C, 66.95; H, 7.48; N, 4.65. $C_{17}H_{23}NO_4$ requires C, 66.86; H, 7.59; N, 4.59%); ν_{max} (neat)/cm^{-1} 3280, 2950, 1755, 1495, 1455, 1390, 1370, 1245, 1090, 1035, 990; δ_H ($CDCl_3$) 1.04 (3H, d, *J* 7.0 Hz), 1.39 (3H, s), 1.44 (1H, dddd, *J* 4.7, 6.3, 10.1, and 13.8 Hz), 1.94 (1H, ddq, *J* 3.1, 10.1, and 7.0 Hz), 2.05 (3H, s), 2.11 (1H, dddd, *J* 3.1, 7.4, 8.1, and 13.8 Hz), 2.69 (1H, dd, *J* 11.4 and 13.2 Hz), 2.86 (1H, dd, *J* 2.9 and 13.2 Hz), 3.77 (1H, dd, *J* 2.9 and 11.4 Hz), 4.11 (1H, ddd, *J* 6.3, 8.1, and 10.6 Hz), 4.19 (1H, ddd, *J* 4.7, 7.4, and 10.6 Hz), 4.73 (1H, br s), 7.18 (2H, d, *J* 8.1 Hz), 7.28 (1H, t, *J* 8.1 Hz), 7.35 (2H, t, *J* 8.1 Hz); *m*/*z* (EI) 246 ($M^+ - OAc$), 214 ($M^+ - CH_2Ph$).

(4*R,5*R**,1′*S**)-4-Isobutyl-5-(3-acetoxy-1-methylpropyl)-5-methyl-1,3-oxazolidin-2-one 6**

Following the procedure previously described, the title compound was prepared from the *syn-trans*-γ-lactone **4** in 73% yield as a colorless oil (Found: C, 61.67; H, 9.29; N, 5.16. $C_{14}H_{25}NO_4$ requires C, 61.75; H, 9.32; N, 5.01%); ν_{max} (neat)/cm^{-1} 3250, 2950, 1750, 1475, 1390, 1370, 1245, 1050, 985; δ_H ($CDCl_3$) 0.94, 0.97 (each 3H, d, *J* 6.8 Hz), 1.04 (3H, d, *J* 7.0 Hz), 1.17 (1H, ddd, *J* 2.4, 10.1, and 14.0 Hz), 1.26 (3H, s), 1.34 (1H, dddd, *J* 4.1, 6.3, 10.5, and 13.0 Hz), 1.55 (1H, ddd, *J* 3.8, 11.2, and 14.0 Hz), 1.63 (1H, m), 1.84 (1H, dddd, *J* 2.4, 7.3, 8.7, and 13.0 Hz), 1.92 (1H, ddq, *J* 2.4, 10.5, and 7.0 Hz), 2.06 (3H, s), 3.67 (1H, dd, *J* 2.4 and 11.2 Hz), 4.06 (1H, ddd, *J* 6.3, 8.7, and 11.0 Hz), 4.19 (1H, ddd, *J* 4.1, 7.3, and 11.0 Hz), 6.49 (1H, br s); *m*/*z* (EI) 212 ($M^+ - OAc$).

(4*R,5*R**,1′*R**)-4-Isobutyl-5-(3-acetoxy-1-methylpropyl)-5-methyl-1,3-oxazolidin-2-one 10**

Following the procedure previously described, the title compound was prepared from the *syn-cis*-γ-lactone **8** in 71% yield as a colorless oil (Found: C, 61.56; H, 9.12; N, 5.21. $C_{14}H_{25}NO_4$ requires C, 61.75; H, 9.32; N, 5.01%); ν_{max} (neat)/cm^{-1} 3250, 2950, 1750, 1475, 1390, 1370, 1245, 1050, 985; δ_H ($CDCl_3$) 0.93, 0.95 (each 3H, d, *J* 6.8 Hz), 0.98 (3H, d, *J* 7.0 Hz), 1.23 (3H, s), 1.24 (1H, m), 1.39 (1H, dddd, *J* 4.8, 6.2, 10.5, and 14.0 Hz), 1.54 (2H, m), 1.89 (1H, ddq, *J* 2.8, 10.5, and 7.0 Hz), 2.04 (3H, s), 2.07 (1H, dddd, *J* 2.8, 7.1, 8.5, and 14.0 Hz), 3.65 (1H, dd, *J* 2.0 and 10.6 Hz), 4.09 (1H, ddd, *J* 6.2, 8.5, and 11.2 Hz), 4.18 (1H, ddd, *J* 4.8, 7.1, and 11.2 Hz), 5.35 (1H, br s); *m*/*z* (EI) 212 ($M^+ - OAc$).

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10 The addition of a large excess of MeOH was essential for the couplings of the α-(alkoxycarbonyl)amino ketones **1** and **3.** Reactions run in the presence of 5 to 20 equiv. of MeOH provided a mixture of unidentified products without any formation of the coupling product. In contrast, the couplings of the α-hydroxy ketone **11** readily took place utilizing 5 equiv. of MeOH. Increasing the amount of MeOH from 5 to 10 or 20 equiv. led to a drop in product yield. The major product in this case was the deoxygenated compound (5-phenylpentan-2-one). See: ref 3(*a*).

11 K. Otsubo, J. Inanaga and M. Yamaguchi, *Tetrahedron Lett.*, 1986, **27**, 5763.

12 In the reductive coupling of the α-hydroxy ketone **11** with the esters of crotonic acid, the *anti-cis*-γ-lactone was isolated as a minor diastereoisomer along with the *syn-cis*-γ-lactone **12.** See: ref 3(*a*).

13 During the intermolecular ketone–olefin couplings mediated by SmI_2 of the α-hydroxy ketone **11** with the esters of crotonic acids, changing the size of the alkyl group of the esters did not affect the diastereoselectivity (*syn*:*anti* = 99:1), but did affect the chemical yield of the γ-lactone **12.** As the size of the alkyl group increased, the amount of the deoxygenated compound (5-phenylpentan-2-one) increased. Especially, the use of *tert*-butyl crotonate produced a substantial decrease in product yield (5%).

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